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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

OTSUKA PHARMACEUTICAL CO., LTD.,

Plaintiff,

v.

SANDOZ, INC., TEVA PHARMACEUTICALS USA, INC., TEVA PHARMACEUTICAL INDUSTRIES LTD., BARR LABORATORIES, INC., BARR PHARMACEUTICALS, INC., APOTEX INC., APOTEX CORP., SUN PHARMACEUTICAL INDUSTRIES, LTD., SYNTHON HOLDING BV, SYNTHON BV, SYNTHON PHARMACEUTICALS, INC., and SYNTHON LABORATORIES, INC.

Defendants.

Consolidated Civil Action No. 3:07-cv-01000 (MLC) (LHG)

Honorable Judge Mary L. Cooper

Magistrate Lois H. Goodman

Document Electronically Filed

DEFENDANTS' POST-TRIAL PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW

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I. INTRODUCTION.

The Hatch-Waxman Act recognizes that some patents used to block pharmaceutical competition are of doubtful validity. *Janssen Pharmaceutica, N.V. v. Apotex, Inc.*, 540 F.3d 1353, 1356 (Fed. Cir. 2008) ("suspect Orange Book listed patents"). The Act, therefore, encourages generic pharmaceutical companies to challenge these patents. *Id.* ("As an incentive for generic pharmaceutical companies to challenge suspect Orange Book listed patents, the Hatch-Waxman Act grants" certain marketing exclusivities to generic pharmaceutical firms.).

Defendants Teva[1] and Apotex are two pharmaceutical companies that filed Abbreviated New Drug Applications ("ANDAs") with the U.S. Food and Drug Administration ("FDA") seeking approval to market generic aripiprazole products for the treatment of schizophrenia. Plaintiff Otsuka Pharmaceutical Co., Ltd. ("Otsuka") listed two patents in the FDA Orange Book as covering aripiprazole: U.S. Patent No. 4,734,416 (issued March 29, 1988) (the "'416 patent") and U.S. Patent No. 5,006,528 (issued April 9, 1991) (the "'528 patent"). Otsuka's earlier '416 patent, entitled "Pharmaceutically Useful Carbostyril Derivatives" (DTX 6), expired on March 29, 2005. Otsuka's later '528 patent, entitled "Carbostyril Derivatives" (DTX 498), is still in force. Defendants challenge the validity and enforceability of the '528 patent.

Otsuka has been able to extend its patent monopoly on aripiprazole for almost an additional decade by obtaining, in the '528 patent, coverage for aripiprazole and its use as an antischizophrenic agent that it already had in the '416 patent. Moreover, aripiprazole is nothing more than an obvious variant of the "unsubstituted butoxy," a compound specifically claimed in

claim 13 of the '416 patent. Under controlling Federal Circuit law, Otsuka is not entitled to extend its period of exclusivity by obtaining a claim in a later patent that is, as here, merely an "obvious modification" of a claim in an earlier patent. *Sun Pharm. Indus., Ltd. v. Eli Lilly & Co.*, 611 F.3d 1381, 1384 (Fed. Cir. 2010); *In re Longi*, 759 F.2d 887, 892-97 (Fed. Cir. 1985). Otsuka's asserted claims 12, 17, and 23 of the '528 patent are, therefore, invalid under the judicially-created doctrine of obviousness-type double patenting. *Id.*

Otsuka's asserted claim 12 (to aripiprazole), claim 17 (to a composition containing aripiprazole), and claim 23 (to aripiprazole's use) as an antischizophrenic agent are also invalid under 35 U.S.C. § 103 for obviousness in view of the prior art. Aripiprazole was the last episode in years of work by Otsuka on a class of compounds called carbostyril derivatives. Otsuka placed most of this work into the public domain before the '528 patent's October 31, 1988 priority date. Otsuka filed for numerous patents (such as the '416 patent, its foreign counterparts, and other patents in the carbostyril field) and published articles and abstracts reporting the testing of carbostyril compounds in animal models and in human clinical trials. Thus, much of Otsuka's work leading to aripiprazole counts *against*, *not for*, patentability because Otsuka published it in the prior art. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 427 (2007) ("[A]dvances, once part of our shared knowledge, define a new threshold from which innovation starts once more."); *Condenser Corp. v. Micamold Radio Corp.*, 145 F.2d 878, 879 (2d Cir. 1944) ("[W]hatever the benefit which the inventor who takes a last step has in fact conferred, he will be credited only with the ingenuity necessary to pass beyond the earlier" steps that are part of the prior art citable against his invention.) (L. Hand). The final increment of

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[1] "Teva" refers to the Teva and Barr defendants. Teva and Barr merged after these actions were filed.

effort needed to get to aripiprazole would have been obvious to one of ordinary skill in the art and involves no more than "ordinary innovation" that is "not the subject of exclusive rights under the patent laws." *KSR*, 550 U.S. at 427. Indeed, no innovation is required, because only routine optimization of prior art compounds is involved. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1367-68 (Fed. Cir. 2007).

In addition, the '528 patent is unenforceable by reason of inequitable conduct arising from Otsuka's failure to disclose information to the Patent Office ("PTO") that refutes arguments Otsuka made to obtain allowance of its patent and false statements in a declaration used to support those arguments.

II. PROCEDURAL HISTORY.

Otsuka brought this consolidated action against Defendants Teva and Apotex alleging infringement of U.S. Patent No. 5,006,528 ("the '528 patent"). (D.I. 13.) The '528 patent is entitled "Carbostyril Derivatives," and is directed to various carbostyril derivative compounds including the compound aripiprazole, which Otsuka markets in the U.S. as Abilify®. (DTX 498).

Teva and Apotex filed Abbreviated New Drug Applications ("ANDA") with the U.S. Food and Drug Administration ("FDA") seeking approval to sell generic aripiprazole products for use in the treatment of schizophrenia. (D.I. 328 ¶¶ 30-33.) Defendants made certifications pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), commonly referred to as a "Paragraph IV certification," asserting that the claims of the '528 patent were invalid, unenforceable, or otherwise not infringed. (D.I. 328 at 10-11, ¶¶ 30-33). Defendants' filing of their ANDAs with the Paragraph IV certifications provides the jurisdictional basis for this lawsuit pursuant to 35 U.S.C. § 271(e)(2)(A). (*Id.* at 3, 10, ¶¶ 1, 30.) This Court has subject matter jurisdiction under 28 U.S.C. §§ 1331 and 1338(a).

Plaintiff Otsuka listed two patents in the FDA Orange Book as covering aripiprazole—the '528 patent and the '416 patent. (DTX 35-A; Nichols 1714:15-1716:3.) The earlier patent, the '416 patent, entitled "Pharmaceutically Useful Carbostyril Derivatives" was filed on March 28, 1979, issued on March 29, 1988, and expired on March 29, 2005. (DTX 6; 35 U.S.C. § 154 (2010).)

The '528 patent was filed on October 20, 1989 and claims priority to a Japanese Application dated October 31, 1988. (DTX 498; D.I. 328 at 9, ¶ 17; Press 103:6-9.) The patent issued on April 9, 1991. (DTX 498; D.I. 328 at 9, ¶ 17.) The first named inventor on the '528 patent is Yasuo Oshiro. (DTX 498; D.I. 328 at 8, ¶ 13.) Unless invalidated or shown to be unenforceable, the '528 patent will not expire until October 20, 2014. There is also a "pediatric exclusivity" period that will prevent generic entry into the market until April 20, 2015. (D.I. 328 at 24, ¶ 56.)[2] The '528 patent term includes a five-year patent term extension granted by the PTO pursuant to 35 U.S.C. § 156. Otsuka's earlier '416 aripiprazole patent is prior art to the '528 patent. (DTX 498, Col. 2:4.)

In this action, Otsuka is asserting claims 12, 17, and 23 of the '528 patent. (D.I. 328 at 9, ¶ 19.) Claim 12 claims the carbostyril compound aripiprazole. It reads: "7-{4-[4-(2,3-Dichlorophenyl)-1-piperazinyl]-butoxy}-3,4-dihydrocarbostyril." (D.I. 328 at 9, ¶ 20; DTX 498, Col. 19:18-19; Press 104-23-106:6; Nichols 1696:15-17.) Claim 17 claims a pharmaceutical composition for treating schizophrenia containing, as the active ingredient, aripiprazole or a pharmaceutically acceptable salt thereof. It reads: "The pharmaceutical composition of claim

[2] Otsuka's "pediatric exclusivity" adds an additional six-month marketing exclusivity. Thus, unless the '528 patent is invalidated or rendered unenforceable in this litigation, the public will not benefit from generic competition for aripiprazole until April 20, 2015.

16,[3] wherein the carbostyril compound or salt thereof is 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy}-3,4-dihydrocarbostyril." (D.I. 328 at 9, ¶ 21; DTX 498, Col. 20:4-7; Press 114:10-19; Nichols 1693:24-1694:5.) Claim 23 claims a method of treating schizophrenia comprising administering a pharmaceutical composition containing, as an active ingredient, aripiprazole or a salt thereof. It reads: "The method of treating schizophrenia of claim 22,[4] wherein the carbostyril compound or salt thereof is 7-(4-[4-(2, 3-dichlorophenyl)-1-piperazinyl]butoxy)-3, 4-dihydrocarbostyril or a salt thereof." (D.I. 328 at 9, ¶ 22; DTX 498, Reexam. Col. 2:13-14; Press 114:22-25; Nichols 1694:6-10.)

Infringement is not at issue in this litigation.[5] Instead, Defendants challenge the validity and enforceability of the '528 patent on three grounds: (1) nonstatutory, obviousness-type double patenting; (2) obviousness under 35 U.S.C. § 103; and (3) inequitable conduct. Defendants also make the contingent argument that the '528 patent would be invalid under §§ 101 and 112 if the Court were to reject their obviousness defense.

III. FINDINGS OF FACT.

A. BACKGROUND ON SCHIZOPHRENIA AND ANTISCHIZOPHRENIA DRUG DISCOVERY.

Schizophrenia is a central nervous system disorder, which in October 1988, was characterized by "positive" and "negative" symptoms. (Castagnoli 612:12-613:10; Roth

[3] Claim 16, from which claim 17 depends, is incorporated by reference into claim 17 and reads: "A pharmaceutical composition for treating schizophrenia containing, as an active ingredient, a carbostyril compound or pharmaceutically acceptable salt thereof of claim **1** and a pharmaceutically acceptable carrier." (DTX 498, Col. 19:26-Col. 20:3.)

[4] Claim 22 reads: "A method of treating schizophrenia in a patient comprising administering a pharmaceutical composition to said patient containing, as an active ingredient, a carbostyril compound or salt thereof of claim 1." (DTX 498, Reexam Col. 2:9-12.)

[5] Defendants have each stipulated that the aripiprazole tablets disclosed in their ANDAs, if commercially made, used, offered for sale or sold in the United States, or commercially imported (continued…)

1033:16-1034:7.) Positive symptoms include hallucinations and delusions, while negative symptoms include flat affect, poverty of speech, inability to experience pleasure, lack of desire to form relationships, and lack of motivation. (Roth 1035:9-15; 1040:14-1041:21; 1417:7-12; Castagnoli 612:17-613:10; *see* Press 77:22-78:19.)

In the 1950s, scientists discovered the function of dopamine as a neurotransmitter in the brain. (Roth 1126:7-23; *see* DTX 362-T at 259; *see* Marshall 328:4-15.) Thereafter, they identified dopamine receptor blockade as the mechanism by which chlorpromazine, a typical anti-schizophrenic drug, treated schizophrenia. (Roth 1126:7-23; *see* PTX 79 at OPC0811755 (Table 2); DTX 362-T at 259.) As a result of this work, a working hypothesis arose that an anti-schizophrenic drug needed to inhibit dopamine transmission in the brain. (Roth 1126:7-23; Castagnoli 614:20-615:11; Beninger 924:21-925:9.)

Prior art drug treatment of schizophrenia included the use of drugs such as chlorpromazine and haloperidol that are classed as "typical" antischizophrenic drugs. (Roth 1128:1-22; PTX 79.) Typical antischizophrenic drugs treat the "positive" symptoms of schizophrenia but not the "negative" symptoms. (Roth 1128:1-22; PTX 79.) Typical antischizophrenic drugs also have problematic side effects, including extrapyramidal symptoms ("EPS"), tardive dyskinesia, prolactin elevation (hyperprolactinemia), and sudden decrease in blood pressure (orthostatic hypotension). (Roth 1128:1-22; PTX 79.) Despite these various drawbacks, the typical antischizophrenic drugs are still used today. (Roth 1128:1-22; PTX 79.) Clozapine was the first "atypical" antischizophrenic drug—atypical in the sense that clozapine had lower EPS liability. (Roth 1148:16-1150:5.) Clozapine, however, can cause a fatal decrease

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into the United States, would fall within the scope of Claims 12, 17 and 23 of the '528 patent to the extent those claims are valid and enforceable. (D.I. 328 at 11, ¶ 35.)

in white blood cells, called agranulocytosis. (*Id.* at 1131:5-25.) Clozapine is still used today, but with careful monitoring of patients that involves frequent blood testing. (*Cf.* PTX 86 (indicating that haloperidol, a typical antipsychotic agent, is still used and that available atypical medications failed to meet the need for an antischizophrenic drug that is better tolerated than earlier typical antischizophrenic drugs).) In 1988, researchers sought to find a drug that would treat both the positive and negative symptoms of schizophrenia, but not cause EPS or agranulocytosis, and that would otherwise have a good side effect profile. (*See* Press 196:6-18; Castagnoli 642:12-643:12; Roth 1390:15-1391:2; *cf.* Roth 1530:25-1532:20 (explaining clozapine's lack of EPS but ability to cause significant adverse effects, such as agranulocytosis); Press 152:10-153:10 (explaining that a compound with the ability to treat the negative symptoms would have interested one of skill in the art in 1988).)

A leading theory to identify potential antischizophrenic drugs in October 1988 was based on the dopamine hypothesis—*i.e.*, that an increased level of dopamine causes symptoms of schizophrenia. (Castagnoli 614:20-615:11; Marshall 331:24-337:3; Beninger 924:21-925:9; Nichols 1675:13-1676:9.) All of the known antipsychotic drugs at the time blocked dopamine receptors in the brain, and many animal test procedures evolved focusing on this hypothesis. (Marshall 332:1-19; Nichols 1533:11-1533:19.)

Common approaches to discovering potential anti-schizophrenic drugs at the time included investigating the ability of test compounds to antagonize the stimulant effects of pro-dopaminergic drugs, such as amphetamine or apomorphine, in rodents. (*See* Marshall 337:15-338:8; Beninger 924:21-925:9; Roth 1072:22-1073:21; *see, e.g.*, Marshall 369:21-370:25; 381:14-382:6; DTX 375.) Apomorphine, for example, was observed to induce a series of

behaviors in rodents, such as increased locomotor activity, climbing, and stereotyped behavior. (*See* Marshall 2183:3-2185:25; Beninger 990:16-991:18; *see, e.g.*, Beninger 925:20-926:17.)

B. THE LEVEL OF SKILL IN THE ART.

Following trial there can be no dispute that the hypothetical "person" of ordinary skill in the art would be highly skilled, with a Ph.D. in organic chemistry, medicinal chemistry and/or pharmacology or in a related field and at least several years of experience designing and/or testing drug compounds. (Press 125:2-12; Marshall 338:19-339:18; Castagnoli 616:5-617:4.) With the exception of Dr. Roth, both sides' experts agreed that the people developing antipsychotic drugs as of 1988 were "high level people" "with a Ph.D. degree and some years of experience." (Nichols 1528:25-1529:5.) For example, Dr. Oshiro, the lead inventor on the '528 patent had a Ph.D. in applied chemistry. (D.I. 328 at 8, ¶ 14.) The hypothetical "person" of ordinary skill in the art in this case would have the knowledge and skill set of a team of individuals with both medicinal chemistry and pharmacology expertise. (Castagnoli 616:5-617:4; 618:1-619:9; Nichols 1709:22-1710:9.)

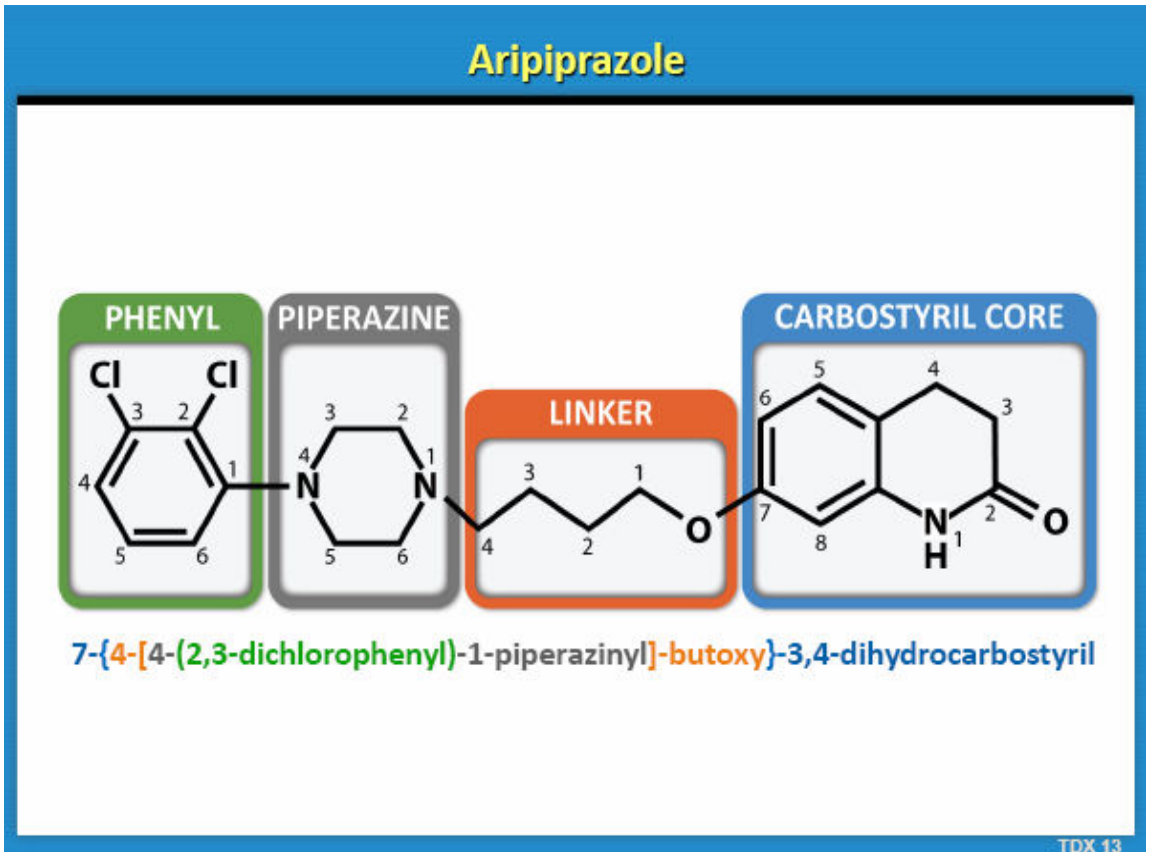
The evidence at trial from both sides' experts showed that in 1988, research in the field of antipsychotic drug discovery and development was performed in multi-disciplinary teams. Each team was led by an individual with a Ph.D. and the team members had expertise in both medicinal chemistry and pharmacology. (Castagnoli 618:1-619:9; Nichols 1709:22-1710:9.) Each person would also have knowledge of adjacent fields—*e.g.*, a medicinal chemist would have an understanding of pharmacology, and vice-versa—and would have the ability to consult with others in such fields. (Castagnoli 618:1-619:9; Nichols 1709:22-1710:9.) Both medicinal chemists and pharmacologists would have a working knowledge of the biological tests that correlate to antipsychotic activity and pertinent side effects of antischizophrenic drugs, including *in vitro* assays and *in vivo* animal models. (*See* Marshall 337:15-338:9; 338:22-339:18.)

Medicinal chemists in particular would be able to use biological test results to observe relationships between systematic changes in molecular structures and corresponding effects on biological activities, and thus elucidate structure-activity relationships ("SAR"). (Press 126:10-127:5.) Persons of ordinary skill in the art used SAR to make informed judgments about the activity that could be expected by changing the structure of a given compound in a particular way.

C. ARIPIPRAZOLE.

The compound at issue here, aripiprazole, belongs to a class of chemical compounds called carbostyril derivatives. (Press 92:13-17.)

The chemical name for aripiprazole is 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]-butoxy}3,4-dihydrocarbostyril. (DTX 498, Col. 19:18-19; Press 104:23-106:6; Nichols 1696:15-17; D.I. 328 at 9, ¶ 20.) The aripiprazole molecule has four parts: a carbostyril core, a butoxy linker, a piperazine group, and a phenyl ring substituted with two chlorine atoms. (*See* Press 92:20-94:22; Nichols 1521:20-1522:24; 1523:4-1524:8; 1524:13-1525:7.) Its structure is depicted in TDX 13 below.



(TDX 13.)

The corners of each of the rings in TDX 13 represent atoms, and the lines connecting the corners represent chemical bonds. (Press 86:20-88:19) Unless otherwise specified, the atom at each corner is carbon. (*Id.*) For ease of reference, the carbon atoms in each ring are numbered according to the conventional nomenclature system used by organic chemists. (Press 95:1-96:11; 108:1-12.) For example, as can be seen above, the carbon atoms of the phenyl ring of aripiprazole are numbered 1 through 6, and the chlorine atoms appear at the 2 and 3 positions.

Two structural features of aripiprazole are particularly relevant to this case. First, aripiprazole's linker has four carbons and is therefore referred to as a "butoxy" linker. (Press 95:1-96:11; 96:18-23; 97:12-98:6.) Second, aripiprazole's phenyl group has chlorine atoms attached at the 2 and 3 positions. (Press 97:12-98:6.) Because it has chlorine atoms at the 2 and

3 positions of the phenyl ring and a butoxy linker, aripiprazole may be referred to as 2,3-dichloro butoxy. (*Id.*)

1. *Otsuka's Prior Art '416 Patent Covered Aripiprazole and Numerous Other Carbostyril Derivatives.*

Otsuka was granted the '416 patent—which covered aripiprazole—on March 29, 1988, less than six months before it filed the Japanese priority application for the '528 patent. (DTX 6; DTX 498; Press 115:21-25; 103:3-9; Nichols 1591:4-6.) The inventors on the '416 patent include Dr. Yasuo Oshiro, who was also an inventor on the '528 patent, Dr. Kazuyuki Nakagawa, and Dr. Kazuo Banno. (*See* DTX 6; DTX 498; Press 104:2-5; 116:1-4; Goolkasian 479:11-12.) It is undisputed that claims 1 and 30 of the '416 patent cover the compound aripiprazole. (Press 115:1-6; 116:5-13; 117:14-120:1; Nichols 1701:13-16; 1716:17-1717:3.)

The '416 patent expired in March 2005. (*See* DTX 6; 35 U.S.C. § 154(c)(1) (2010).) By the time the '416 patent expired, Otsuka had received a full seventeen years of patent protection that precluded others from making, using, or selling aripiprazole. (*Id.*; *see also* Press 173:21-174:5.) Otsuka took advantage of that blocking patent position to make sure that no one else could market aripiprazole. In its NDA seeking approval to market Abilify®, Otsuka certified to the FDA that the '416 patent covered its aripiprazole products. (DTX 35-A; Nichols 1714:11-1716:14.) Otsuka also listed the '416 patent on its Abilify® package insert, which put the public on notice that Otsuka could assert the '416 patent against anyone who tried to enter the market with an aripiprazole product. (DTX 553 at OPC0796420; Nichols 1718:3-1719:4.)

The '416 patent (together with other patents that Otsuka owned on carbostyril derivative compounds (*e.g.*, DTX 20 (U.S. Patent No. 4,619,932)) also effectively prevented other companies from developing and commercializing carbostyril derivative compounds. (Press 116:14-117:5; 173:21-174:5; 174:11-23; 190:8-20 (explaining from personal experience that

after his former company, Lederle, lost a patent interference for claims to the drug olanzapine, it was left "[w]ithout the ability to protect [its] work" and within a short time its "antipsychotic program was shut down."); Nichols 1710:18-1714:10 (agreeing that the patent landscape could impact a company's decision whether to continue development of a particular compound).)

The '416 patent includes broad claims that Otsuka's experts contend took billions if not trillions of compounds out of the public domain. (DTX 6; Nichols 1624:8-1626:3; 1700:6-1701:12; 1716:17-24; Roth 1241:9-22.)

The '416 patent specification contains broad disclosure of the uses of the compounds encompassed by the patent and includes a specific teaching that the compounds are useful as central nervous controlling agents, including antischizophrenia agents. (DTX 6 at Col. 3:13-16; Press 120:15-121:5.) The specification also states that the claimed compounds were tested in several animal models. (*Id.*)

> Furthermore, as to the central nervous controlling activities, the present compounds have various pharmacological activities such as muscle relaxing action, **apomorphine-vomiting inhibitory action**, ptosis action, hypothermy action, **spontaneous movement controlling action**, hypermotion controlling action of rats, **anti-methanphetamine action**, **methanphetamine group toxicities lowering action**, analgetic action and anti-noradrenaline action but they have only weak activities in anticholine action, cardio-inhibitory action and catalepsy inducing action. Therefore, compounds of the present invention are useful for central nervous controlling agents such as central muscle relaxing agents, sleep-inducing agents, pre-operative drugs, **antischizophrenia agents**, sedatives, antianxiety drugs, anti-manic depressive psychosis agents, antipyretic agents, analgetic agents and depressors, without showing side-effects such as the feeling of thirst, constipation, tachycordia, parkinsonism, and/or delayed dyscinesia which exist with conventional central nervous controlling agents.

(DTX 6 at Col. 3:13-22 (emphasis added).)

As Dr. Press testified, several of the animal models on this list are used to predict antischizophrenic activity, including tests for apomorphine vomiting inhibitory action, the spontaneous movement of rats, anti-methamphetamine action, and methamphetamine group

toxicity. (*Id.*; Press 121:6-123:3; 225:1-228:3.) Dr. Press used and interpreted the results of these animal models during his own research on antischizophrenic drugs. (Press 122:23-123:17.) The '416 patent also provides actual test data in Table II and III for the halothane anesthesia test. Otsuka used the halothane anesthesia test to predict whether compounds would have antischizophrenic activity. (Oshiro 1846:9-19; 1849:24-1852:8; DTX 208-T.)

D. HOW OTSUKA OBTAINED ITS SECOND PATENT ON ARIPIPRAZOLE.

1. *What the '528 Patent Claims and Describes.*

The '528 patent is directed to carbostyril derivatives and the use of those compounds to treat schizophrenia. (DTX 498; Press 104:6-8; Marshall 338:12-18.) The '528 patent claims aripiprazole along with a number of butoxy-linked carbostyril derivative compounds that are structurally very similar to aripiprazole, including a 2-chloro, 3-methyl phenyl substituted compound, and a double-bonded ("carbostyril" or "dehydrocarbostyril" as opposed to dihydro carbostyril) version of aripiprazole (represented by a dotted line at the 3,4 position on the carbostyril skeleton). (DTX 498 at Col. 12:Table 2 (Example 3), Col. 13:Table 2 (Example 10), Col. 17:55-18:36 (Claim 1); Nichols 1729:2-1732:10.)[6]

The '528 patent contains no human data to support its claims to the treatment of schizophrenia. (Nichols 1726:20-22.) More specifically, the '528 patent contains no human clinical data indicating that aripiprazole treats positive symptoms or negative symptoms of schizophrenia. (Nichols 1726:20-1727:14.)

[6] According to the FDA approved label for Otsuka's commercial aripiprazole product, aripiprazole metabolizes into the double-bonded version of aripiprazole in the body. The double-bonded or dehydro version of aripiprazole is active in the body and has affinities for the D_2 receptors similar to those of aripiprazole. The dehydro-aripiprazole represents 40 percent of the total drug exposure in the plasma. (DTX 564 at 56; Nichols 1733:21-1735:2.)

Moreover, the patent includes data from only two animal tests, the anti-apomorphine stereotypy test in mice and anti-epinephrine lethality test in mice. (DTX 498 at Table 3 (Cols. 16-17); Nichols 1727:15-23.) The anti-epinephrine lethality test demonstrates activity at alpha-adrenergic receptors and correlates to a side effect called orthostatic hypotension. (DTX 498 at Col. 1:62-65; Nichols 1727:21-23.) The patent contains no specific test for other side effects such as agranulocytosis or EPS. (Nichols 1727:18-1728:9.) The anti-apomorphine stereotypy test is the only test in the '528 patent that correlates to antipsychotic activity. The '528 patent describes the claimed carbostyril derivatives as having strong activity for blocking neurotransmission of dopaminergic receptor and weak alpha-blocking activity. (DTX 498 at Col. 3:26-41.) No other neurologic receptors are discussed in the patent, which for example, says nothing about targeting serotonin or muscarinic receptors. (DTX 498; Nichols 1726:11-19.)

2. *Otsuka Obtained Its Second Patent on Aripiprazole by Arguing That Butoxy-Linked Carbostyril Derivative Compounds Were Unexpectedly Superior to Propoxy-Linked Compounds.*

To obtain the '528 patent, Otsuka's second patent on aripiprazole, Otsuka argued that a person of ordinary skill in the art would not have expected that butoxy (4-carbon) linked compounds would be more potent than propoxy (3-carbon) linked versions of the otherwise identical molecules, and that the structurally similar unsubstituted butoxy and 2,3-dichloro propoxy prior art compounds would not have been expected to exhibit antischizophrenic activity. Publicly available prior art demonstrates that the increased potency of the butoxy-linked compound would have been expected. (*See, e.g.*, DTX 214; DTX 1159-T.) Otsuka was aware of this prior art, but did not disclose it to the PTO. By not disclosing this highly relevant prior art, Otsuka deprived the PTO of the ability to fairly evaluate the properties of Otsuka's compounds claimed in the '528 patent against the compounds disclosed in the prior art.

a. Otsuka Requested a Reexamination of the '528 Patent.

Otsuka requested that the PTO reexamine the '528 patent in an evident attempt to prepare the patent for litigation.[7] Otsuka's reexamination request stated that the '416 patent, and other Otsuka patents and publications, raised a "substantial new question of patentability" with regard to the claims of the '528 patent. (DTX 121 at 00004-25.) Otsuka admitted to the PTO that the compounds of the '416 patent are "disclosed as having central nervous controlling effects" and "it can be argued that the use of the described compounds as antischizophrenia agents is specifically contemplated." (DTX 121 at 00004-25.)

The examiner repeatedly rejected all the '528 patent claims for obviousness based on compounds disclosed in Otsuka's own prior art patent documents, including the '416 patent (specifically the unsubstituted butoxy) and the DE '105 German patent (specifically the 2,3-dichloro propoxy). (DTX 121 at 01144-51, 01235-51, 1320-34) The examiner found that "it would have been obvious for one of [ordinary] skill in the art to make slight modifications to obtain the compounds of the invention." (DTX 121 at 01235-51, 01328) Otsuka's arguments failed to change the examiner's mind, and a final rejection was issued. (DTX 121 at 01320-34.)

Otsuka told the reexamination examiner that there was "no evidence" that the unsubstituted butoxy may be useful in treating schizophrenia. (Oshiro 1880:20-1881:14; 1882:6-15; 1883:15-1884:4; DTX 121 at 01274, 01280, 01348; DTX 459 at OPC0001554, OPC0001560.)

[7] Under 35 U.S.C. §§ 302-307 an issued patent may be reexamined by the PTO if there is a "substantial new question of patentability" that had not been dealt with during the original prosecution. If there is such a new question, the patent is again examined by the PTO for patentability. The PTO may find the patent unpatentable or confirm its patentability in either its original form or as amended during the reexamination process.

Following the final rejection, Otsuka submitted a declaration by Otsuka's employee, Dr. Hirose ("the Hirose Declaration"). (DTX 4; DTX 399; DTX 121 at 01342-64.) The Hirose Declaration presented animal test results that purported to show "unexpected" superiority of the claimed compounds over Otsuka's prior art carbostyril derivatives based on the change from a "propoxy" linker disclosed in the prior art to a "butoxy" linker. The change in the length of the linker, from propoxy to butoxy, is the sole difference between Otsuka's prior art 2,3-dichloro propoxy compound and aripiprazole. Dr. Hirose did not test the structurally similar unsubstituted butoxy.

Based on Dr. Hirose's test results, Otsuka argued that there was an "unexpected" improvement in changing from a propoxy to butoxy linker. (DTX 4 at 14.) The reexamination examiner's statement of "Reasons for Patentability/Confirmation" demonstrates that she relied on the Hirose Declaration and was persuaded by Otsuka's assertion of "unexpected" superiority:

> The compounds [of] claims 1-21 are found to be allowable since applicants have compared their compounds with the closest prior art. The ones with just one difference in the linker chain, propyloxy [a/k/a propoxy] to a butoxy chanin [sic, chain] shows a clear unexpected result in the ED50 values.

(DTX 121 at 01412.)

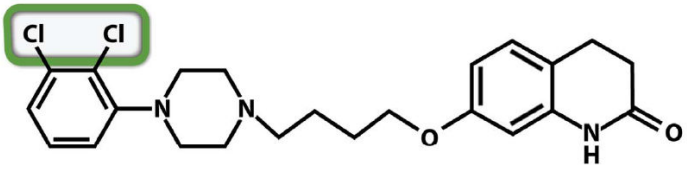
In other words, as the PTO saw it, aripiprazole is unpatentable unless an improvement in going from propoxy to butoxy was "unexpected." (*Id.*)

A person of ordinary skill in the art would have had access to more information than the examiner of the '528 patent. This information disclosed that the allegedly unexpected results were actually expected.

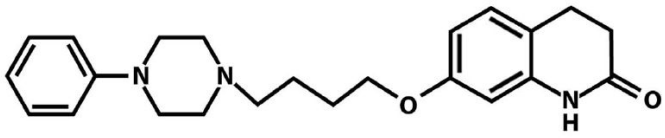
E. THE SCOPE AND CONTENT OF THE PRIOR ART.

1. *The '416 Patent and Nakagawa Declaration Disclose That the Unsubstituted Butoxy Carbostyril Analog of Aripiprazole Has Antischizophrenic Activity.*

The prior art unsubstituted butoxy compound is disclosed at Col. 6, lines 41-42 of Otsuka's prior art '416 patent and is expressly claimed in claim 13 of that patent. (DTX 6, Col. 6:41-42, Col. 70:62-63; Press 99:18-101:2; 120:2-4; 158:1-4.) It also is test compound no. 41 in the prior art declaration of Kazuyuki Nakagawa ("the Nakagawa Declaration"), which Otsuka submitted to the PTO during the prosecution of the '416 patent and is part of the prosecution history of that patent. (DTX 214; Press 133:5-7.) The unsubstituted butoxy compound is identical to aripiprazole with the single exception that the phenyl ring of the unsubstituted butoxy does not have any substituents, whereas the phenyl ring of aripiprazole has chlorine atoms at the 2 and 3 positions. (Press 99:18-101:2.)



Aripiprazole



Unsubstituted Butoxy

(TDX 10.)

The '416 patent specification and its prosecution history teach the unsubstituted butoxy's usefulness as an antischizophrenic agent. For example, the '416 patent teaches that its claimed

compounds "are useful for central nervous controlling agents such as . . . antischizophrenia agents." (DTX 6 at 3:13-16; Press 120:15-121:5.)

a. The Mouse Jumping Test in the Nakagawa Declaration Was a Test Known for Antischizophrenic Activity.

The Nakagawa Declaration[8] that Otsuka presented to the PTO in support of its application for the '416 patent contained data for the unsubstituted butoxy (test compound 41) in a test for mouse jumping ("Mouse Jumping Test"). (DTX 214 at 12.) The declaration concluded that the unsubstituted butoxy compound and the other tested compounds "perform excellent in activity for jumping behavior in mouse induced by Methamphetamine and L-Dopa" over the cited prior art. (DTX 214 at 14; Press 131:18-25; 133:5-7.)

As Otsuka's expert Dr. Nichols admitted on questioning from the Court, the Mouse Jumping Test in the Nakagawa Declaration Table 8 was testing for antipsychotic activity of the tested compounds.

> THE COURT: But this particular test, what property were they trying to demonstrate, whether or not you think they succeeded?
>
> THE WITNESS: My understanding is that they did use this test as a predictor of potential antipsychotic activity.

(Nichols 1642:5-9.)

The Mouse Jumping Test was well known at the time to be a test of a compound's antischizophrenic potential. (*See* DTX 375 ("Lal article") at 670-71; DTX 471 at 4; Press 130:11-131:3; Marshall 365:16-367:23; 381:14-25; 388:5-390:2; 2167:1-2193:2; Banno Dep. 120:6-23, July 16, 2008; Kikuchi Dep. 106:24-107:15, May 28, 2008.) This inhibition of mouse

[8] The Nakagawa declaration is prior art to the '528 patent. It became public at the same time the '416 patent issued on March 29, 1988, more than one year prior to the October 20, 1989 U.S. filing date of the '528 patent. 37 C.F.R. § 1.11 (1988); Manual of Patent Examining Procedure ("MPEP") § 103 (5th ed., Rev. 8, 1988); (Press 129:13-16.)

jumping to antischizophrenia correlation was demonstrated by the Lal article, which showed that known antischizophrenic drugs and D_2 antagonists such as haloperidol, pimozide, chlorpromazine, thioridazine and clozapine all blocked jumping behavior. (Marshall 2191:25-2193:2; DTX 375 at 670 (Table 1).) These mouse jumping test results on these known antischizophrenic drugs correlated to stereotypy test results for some of these same drugs. (Marshall 2189:23-2194:9 (explaining DTX 375 (Lal) and DTX 509 (Creese).)

Otsuka itself used the Mouse Jumping Test to screen compounds for antischizophrenic activity. Dr. Banno, the first named inventor on the '416 patent and former head of the group performing antischizophrenic drug discovery at Otsuka, testified in designated deposition testimony that the "[Mouse Jumping Test] was certainly one of the important tests for [the] determination [of potential antipsychotic activity]." (Banno Dep. 14:21-14:23; 15:8-15:9; 15:11-15:17; 15:19-15:21; 15:24-16:1; 35:15-36:2; 120:19-23.) Dr. Takashi Hiyama, who was chief of the pharmacology department at Otsuka, likewise testified in designated deposition testimony that he selected the Mouse Jumping Test to screen for a new antischizophrenic drug. (Hiyama Dep.10:11-16, 10:23-11:14, 13:4-19, 18:10-19:6, 19:9-10; 94:5-21.) Dr. Tetsuro Kikuchi, an Otsuka pharmacologist who headed the project devoted to developing new antipsychotics, also testified in designated deposition testimony that a positive result in the Mouse Jumping Test correlated to D_2 antagonist activity. (Kikuchi Dep.14:11-15:16, 15:18-16:2, 16:4-14, 16:16-17:1, 17:3-7; 24:16-25:3, 61:4-61:7, 61:10-61:14, 61:16-62:4; 108:18-109:3; 109:7-11.)

Otsuka's counsel, Thomas Irving of the law firm of Finnegan, Henderson, Farabow, Garrett & Dunner, LLP (the "Finnegan firm") represented to the PTO during prosecution of U.S. Patent No. 4,619,932 (the "'932 patent"), another Otsuka patent directed to carbostyril

derivatives, that the Mouse Jumping Test was a test of a compound's antischizophrenic activity. (Press 130:11-131:3; Marshall 388:5-390:2.)

> Specifically, he wrote:
>
> A test method for determining whether a compound will have anti-schizophrenic activity is set forth on pp. 85-86 of the Specification. This test determines the activity for inhibiting jumping behavior in mice induced by methamphetamine and L-DOPA [the Mouse Jumping Test].
>
> There are compounds tested and reported in Table 2 at pp.86-87 of the Specification which fall within the Scope of the claimed invention. It is evidence from Table 2 that such carbostyril derivatives are useful as anti-schizophrenic agents.
>
> Therefore, all the test data of record demonstrate that the claimed compounds have an anti-schizophrenic activity and provide reasonable assurance, assuming arguendo that such assurance is required, that the claimed compounds have anti-schizophrenia activity. One of ordinary skill in the art can use the claimed compounds as anti-schizophrenic agents without engaging in undue experimentation.

(DTX 471 at 4; Press 130:11-131:3; Marshall 388:5-390:2.)

Researchers outside Otsuka also used the Mouse Jumping Test to screen compounds for potential antischizophrenic activity. (*See* DTX 375; DTX 581.) For example, Eli Lilly & Company reported results from a Mouse Jumping Test in a patent directed to potential neuroleptic compounds. (Roth 1376:9-1377:6; 1383:16-1384:6.)

b. The Nakagawa Declaration Teaches That the Unsubstituted Butoxy Would Have Been Expected to Have Antischizophrenic Activity, Not Just Antihistaminic Activity.

Otsuka contends that the '416 patent discloses that the unsubstituted butoxy only has antihistaminic activity. This argument is refuted by the Nakagawa Declaration that reported Mouse Jumping Test data to support the conclusion that the unsubstituted butoxy has "excellent" activity as a potential antipsychotic compound, as well as the Lal paper (DTX 375) and testimony of Drs. Marshall and Nichols which confirm that the Mouse Jumping Test is a test of

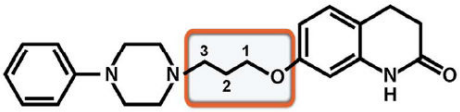
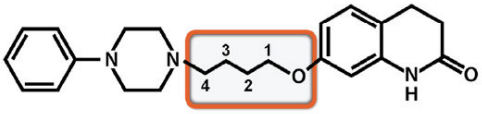
antipsychotic activity. Further, in previous interference proceedings involving the '416 patent, Otsuka presented testimony to the PTO that a person of ordinary skill would understand from the '416 patent that *all* of the claimed compounds (including the unsubstituted butoxy) have *both* antihistaminic and central nervous system controlling activity. (Bodor Dep. 12:11-13:13 (stating that the '416 patent specification indicates "that all the compounds covered by general formula 1 have both antihistaminic and central nervous controlling effect.").) Dr. Bodor further testified that "it is well-known that antihistaminic agents generally have central nervous system effects," and that based on his "knowledge and background in the field of medicinal chemistry" he would not have any reason to doubt that the carbostyril derivatives disclosed in the '416 patent specification "possess both antihistaminic activity and central nervous controlling activity." (*Id.* at 14:2-13.)

Accordingly, a person of ordinary skill in the art would have expected the unsubstituted butoxy compound to exhibit antipsychotic activity.

2. *The Nakagawa Declaration Teaches That 7-Linked Butoxy Compounds Are More Potent Than 7-Linked Propoxy Compounds.*

The Nakagawa Declaration's Mouse Jumping Test data includes a head-to-head comparison between the unsubsituted *propoxy* carbostyril compound that had an ED_{50}[9] value of 9.3 mg/kg and the next adjacent homolog, the unsubstituted *butoxy* carbostyril compound that had an ED_{50} value of 5.5. (DTX 214; DTX 208-T at OPC0616309 (corroborates accuracy of 5.5 ED_{50} value for unsubstituted butoxy in the Nakagawa Declaration); Press 134:15-135:15; 140:22-141:10; Goolkasian 537:8-538:1; Castagnoli 671:11-672:14; Oshiro 1848:7-1849:11; 1852:9-1853:18; 1867:8-1870:1.)

[9] ED_{50} is a measure of potency that establishes the effective dose that gives you a 50 percent effect. (Press 132:6-22; Roth 1072:12-14.)

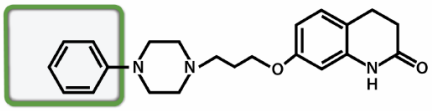
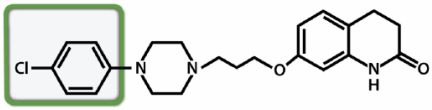
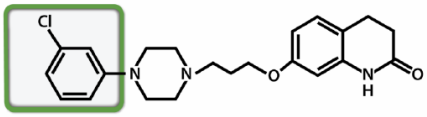
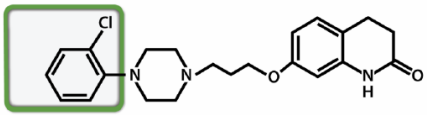
No.	Compound	Name	ED_{50}
6		Unsubstituted Propoxy	9.3
41		Unsubstituted Butoxy	5.5

(ADX 08 (DTX 214 at 14 (Table 8).)

A lower ED_{50} value in the Mouse Jumping Test means greater antischizophrenic potency. Thus, the results show that the change from a propoxy linker to a butoxy linker increases antischizophrenic potency. (Press 134:17-135:15; Castagnoli 671:11-672:14.) This structure-activity data in the Nakagawa declaration would have taught a person of ordinary skill that he or she could reasonably expect to increase antischizophrenic potency by changing from a propoxy linker to a butoxy linker. (Press 134:17-135:15; Castagnoli 671:11-672:14.)

3. ***The Nakagawa Declaration Teaches That Adding Chlorine at the 2 and the 3 Position on the Phenyl Ring Increases Antischizophrenic Potency.***

The Mouse Jumping Data from the Nakagawa Declaration would also point the person of ordinary skill directly towards the addition of chlorine at the 2 and 3 positions on the phenyl ring. (Press 135:18-137:14; 137:14-138:4.) It includes Mouse Jumping Test data for propoxy linked compounds that are unsubstituted (compound 6), and for propoxy linked compounds that include chlorine substituents at the 2, 3, and 4 positions on the phenyl ring (compounds 43, 39, and 16, respectively). (Press 135:18-136:7.) The structures of these four compounds and their ED_{50} values are shown in TDX 23:

No.	Compound	Name	ED_{50}
6		Unsubstituted Propoxy	9.3
16		7-(4-chloro)propoxy	15.1
39		7-(3-chloro)propoxy	2.5
43		7-(2-chloro)propoxy	3.4

(TDX 23 (citing DTX 214, Table 8 at 14).)

The unsubstituted propoxy (compound 6) has an ED_{50} of 9.3 mg/kg, while the 2-chloro, 3-chloro, and 4-chloro propoxy have ED_{50} values of 3.4 (compound 43), 2.5 (compound 39), and 15.1 mg/kg (compounds 16), respectively. Thus, substituting a chlorine atom at the 2 position or the 3 position of the phenyl ring *increases* antischizophrenic potency. On the other hand, substituting a chlorine atom at the 4 position of the phenyl ring *decreases* antischizophrenic potency. (Press 136:8-137:3; Castagnoli 736:12-737:24.)

Because the propoxy and butoxy linked compounds are homologs, the person of ordinary skill would reasonably expect that they behave similarly, and that a butoxy compound with chlorines at the 2 and/or 3 positions would likewise be more potent than the unsubstituted butoxy. As Dr. Press testified:

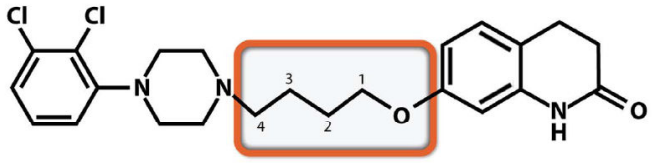
> Q. Why would the person of ordinary skill in the art use the data from the propoxy series of compounds to make the butoxy series of compounds?
> A. Medicinal chemistry works by a set of rules and a set of assumptions, and the assumption throughout this work is that these are not unrelated events. Not only do we make compounds in a systematic way, but the results we get from the systematic changes teach you something that can be

> generalized and learned and applied to related compounds. And so propoxy to butoxy is a very related compound. Unsubstituted butoxy and unsubstituted propoxy we've already seen earlier are very similar compounds. And a medicinal chemist would expect that the chlorine substitution learned on the propoxy series would be directly applicable to the butoxy series.

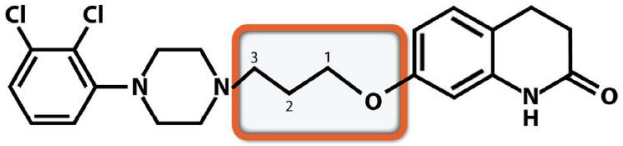
(Press 137:15-138:4.)

4. ***Foreign Counterparts to Otsuka's '416 Patent Disclosed the 2,3-Dichloro Propoxy and Disclosed That Such Compounds Are Useful as Antischizophrenia Agents.***

The prior art 2,3-dichloro propoxy compound is the same as aripiprazole except it has a "propoxy" linker with three methylene (-CH_2-) links, whereas aripiprazole has a "butoxy" linker with four methylene (-CH_2-) links. (Press 96:18-23; 97:2-11.)



2,3-Dichloro Butoxy [Aripiprazole]



2,3-Dichloro Propoxy

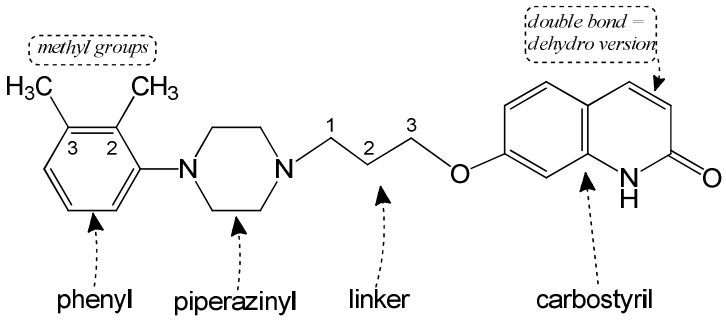
(TDX 8.)

The 2,3-dichloro propoxy compound is Example 317 in Otsuka's prior art German patent no. 2,912,105 ("DE '105"). (DTX 248-T at 68.) This 2,3-dichloro propoxy compound also appears in Otsuka's prior art SE '945 Swedish published patent application in Example 134. (DTX 1159-T at 60-62.) SE '945 specifically states that its compounds are useful as antipsychotic and antischizophrenia agents yet cause fewer side effects such as parkinsonism.

(DTX 1159-T at 5 ("**The compounds of the present invention** are therefore **useful** as **means of controlling the central nervous system** as muscle relaxants, sleeping agents, presurgery drugs, **antischizophrenia agents**, sedatives, **anxiolytics**, drugs for **manic-depressive psychosis**, fever-lowering agents, analgesics and "depressors" without showing side effects such as thirst, constipation, tachycardia, parkinsonism and/or delayed dyschezia, which are displayed by conventional agents which acton the central nervous system." (emphasis added)).) Both DE '105 and SE '945 are foreign counterparts of the '416 patent.

5. *OPC-4392 Was a Promising Antischizophrenic Drug That Had Been Tested in Phase II Human Clinical Trials.*

The prior art carbostyril derivative OPC-4392 has the following structural features:

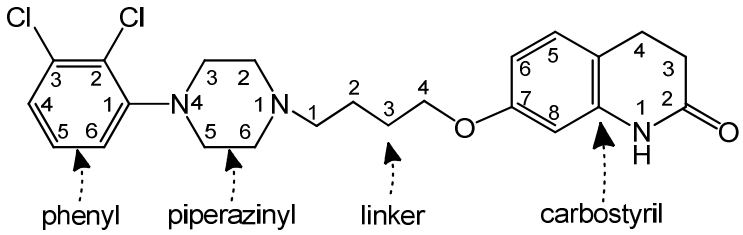


OPC-4392

The carbostyril derivative compounds primarily at issue in this case come in two forms, the double bond version ("dehydro") and the single bond version ("dihydro"). (Castagnoli 663:22-664:23.) OPC-4392 is the double bond version as shown by the twin diagonal lines in the upper right portion of the carbostyril group. (*Id.* at 662:5-663:11.) OPC-4392 has a "propoxy" linker because of the three carbon links in it. (Press 145:22-146:17.) In the drawing for OPC-4392 two lines stick out from the top of the phenyl ring leading to CH_3 groups. (*See id.*) These CH_3 groups are called "methyl" substituents. (*See id.*) These methyl substituents are

attached at the 2 and 3 positions. (*See id.*) Thus, OPC-4392 is said to be 2,3-dimethyl substituted. (*Id.*)

The only differences between OPC-4392 and aripiprazole are that: (1) aripiprazole has a four link butoxy linker, rather than a three link propoxy linker; (2) aripiprazole has chlorines (Cl), rather than methyls (CH_3), at positions 2 and 3 on the phenyl ring; and (3) aripiprazole has a single bond, rather than a double bond in the carbostyril group. (Castagnoli 658:14-661:24.)



aripiprazole

History reveals that aripiprazole was in fact derived from OPC-4392. (DTX 362-T at 1 (It "all started from OPC-4392."); at 5 ("I would like to emphasize the importance of the development of OPC-4392 that had served as the basis for OPC-14597 [aripiprazole]").) Prior to the '528 patent filing date, there was ample published information about OPC-4392. This information included extensive animal test data and reports on what happened with OPC-4392 in Phase I and II human clinical trials.[10] (PTX 545; DTX 104 at OPC0791807-08; DTX 377-T; DTX 388-T; *see* Press 150:25-151:25.) This data would suggest to a person of ordinary skill in the art the benefits of attaching the linker at the 7-position on the carbostyril core and of a 2, 3 di-substitution pattern on the phenyl ring. (Castagnoli 660:24-661:24; 661:7-14; Press 150:25-151:25; 163:4-16.)

[10] OPC-4392 made it into Phase III clinical tests as well, but those were not early enough to be prior art. (DTX 362-T at OPC0739934.)

DTX 104, a March 14, 1988 article by Otsuka's Dr. Yasuda, reports on some of the animal test results for OPC-4392. It reported that OPC-4392 was active both as a presynaptic dopamine autoreceptor agonist and as a post synaptic dopamine antagonist. (DTX 104 at 1952 (Table VII).) In particular, OPC-4392 was reported as having a positive score in the GBL test for presynaptic agonism and in the stereotypy and climbing tests in mice for dopamine post synaptic antagonism. (DTX 104 at 1952; Castagnoli 636:12-637:9; Roth 1401:23-1403:22.) The article goes on to explain that:

> It has been proposed that apomorphine-evoked stereotyped behavior and climbing behavior in mice results from the activation of postsynaptic dopamine receptors. The fact that OPC-4392, as well as dopamine antagonists, inhibit these behaviors induced by apomorphine suggests that OPC-4392 may act as an antagonist at postsynaptic dopamine receptors in vitro and in vivo.

(DTX 104 at 1953 (internal reference citations omitted).)

The article then concludes:

> In conclusion, OPC-4392 appears to act as an agonist at presynaptic dopmine [sic dopamine] autoreceptors associated with dopamine synthesis and as an antagonist at postsynaptic D2 receptors as determined by a series of behavioral and biochemical tests that are indicative of dopaminergic function.

(*Id.*)

In addition to its strong animal test profile, OPC-4392 also would have caught the eye of the ordinary researcher because the prior art published literature reveals that OPC-4392 had a number of very favorable characteristics in humans. (PTX 545; DTX 388-T at 1517; *see* Press 150:25-154:19; Castagnoli 625:13-627:23.) Data about what happens in humans is particularly noteworthy because schizophrenia is a human disease not known to occur in animals. (Castagnoli 620:13-622:6; Roth 1187:20-24.) One article, M. Murasaki et al., *A Phase I Study of a New Antipsychotic Drug, OPC-4392*, 12 PROG. NEURO-PSYCHOPHARMACOL. & BIOL. PSYCHIAT. 793 (1988) (PTX 545), reported on the results of a Phase I human clinical trial with

OPC-4392. The article concluded that "[j]udging from the results of the present study, OPC-4392 was ascertained to be safe and to have a conspicuous characteristic which had quite a different effect upon the serum prolactin level from that of conventional antipsychotic drugs. Therefore, OPC-4392 is expected to have some advantageous effects different from those of conventional antipsychotic drugs." (PTX 545 at 802.)

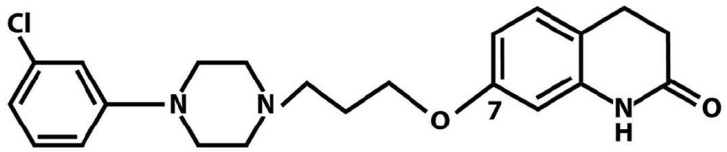
The 1987 Murasaki article (DTX 388-T) reported, based on the results of Phase II clinical tests in humans, that OPC-4392 had some activity in ameliorating the positive symptoms of schizophrenia, although it was "not strong" in that regard. (DTX 388-T at 1517; Press 150:24-151:25.) It also concluded that in clinical tests in humans OPC-4392 was particularly strong in relieving the negative symptoms of schizophrenia, and had a good side effect profile with respect to EPS, blood prolactin levels, and orthostatic hypotension. (DTX 388-T at 1517; Press 153:22-156:1; Castagnoli 627:7-23; 620:13-622:19.) There was also no indication that agranulocytosis would develop. (*See id.*) Sometimes there were side effects such as nausea, but these were not life-threatening and did not prevent its administration to humans. (*See* Press 155:14-156:1; Castagnoli 627:25-628:15.) In short, OPC-4392 had all the characteristics sought in an antischizophrenic drug, save only that its effect on positive symptoms was "not strong." (Castagnoli 625:13-626:1; Press 150:25-156:1.)

A later article by Gerbaldo, published November, 1988 (one month too late to be prior art but still reflecting the results of clinical research that was going on in the prior art) reported that OPC-4392 treated hallucinations (a positive symptom of schizophrenia) in "4 out of 4 cases." (DTX 394 at 388.) The Gerbaldo article also reported OPC-4392 improved negative schizophrenia symptoms. (*Id.*) ("In conclusion, the clinical effects of OPC-4392 in patients with a schizophrenic disorder indicate that particularly, the negative symptoms improve.").)

In an article published in 1993 by Duval *et al.*, researchers in Europe still classified OPC-4392 as a "promising alternative in the treatment of schizophrenic syndromes." (DTX 396 at 180; Roth 1421:1-21 ("They're classifying it as a promising alternative, yes.").) While this article is too late to be considered by the hypothetical skilled person in 1988, it is evidence of how skilled persons still believed that OPC-4392 was a promising drug only a few years later.

6. *OPC-4139 Was a 3-Chloro Propoxy Compound for Which Otsuka Disclosed Promising Preclinical Data.*

A 1981 publication from the Eighth International Congress of Pharmacology included an an Otsuka abstract authored by T. Hiyama. (DTX 514 at 380.) The abstract disclosed a 3-chloro propoxy carbostyril derivative compound called OPC-4139, which was described as "a new synthetic compound" that preclinically has been shown to have "similar pharmacological actions to conventional neuroleptics." (*Id.*) The structure of OPC-4139 differs from aripiprazole only in that it has a propoxy linker and lacks a chlorine at the 2 position on the phenyl ring. (Press 144:21-146:10.)



OPC-4139

(TDX 26.)

The compound was found to inhibit jumping behavior of mice induced by L-Dopa and methamphetamine and lacked cataleptogenic action (a test that indicatd it had low propensity for EPS side effects). (DTX 514 at 380; Roth 1130:2-9 (explaining that catalepsy action in rodents correlates to EPS side effects).) The compound also was found to have inhibited apomophine-induced climbing behavior in mice, but did not antagonize apomorphine-induced stereotypy in

rats (no information was given on whether the compound inhibited stereotypy behavior in mice). (DTX 514 at 380; Roth 1280:21-1281:15.) In his testimony, Dr. Oshiro indicated that Otsuka preferred to use mouse apomorphine-induced stereotypy testing rather than rat stereotypy testing because the rats metabolized the carbostyril derivative compounds too quickly and the mouse stereotypy tests provided results more analogous to activity in humans. (Oshiro 1751:1-16.) Thus, the fact that OPC-4139 did not inhibit stereotypy behavior in rats does not mean that it was inactive as a D_2 antagonist. (Oshiro 1751:1-16; Marshall 2187:4-2189:3 (discussing false negatives and false positives in stereotypy testing and the potential effects of species differences).) From the data presented in the abstract, the authors concluded that "OPC-4139 is potent in suppressing the dopaminergic activity." (*Id.*; Marshall 2181:12-2183:1 (interpreting this data as indicative of OPC-4139 acting as a post-synaptic D_2 antagonist).) The Hiyama abstract would have taught a person of ordinary skill in the art the benefits of including a chlorine at the 3 position on the phenyl ring. (DTX 514 at 380.)

7. *The '932 Patent Discloses Efficacy and Side Effect Information for Earlier Otsuka Carbostyril Derivatives.*

Otsuka's prior art U.S. Patent No. 4,619,932 ("the '932 patent") (DTX 20), disclosed a series of Otsuka's earlier carbostyril derivative compounds that had alkyl rather than alkoxy linkers that were typically attached at the 6 rather than the 7 position on the carbostyril skeleton. The '932 patent contains Mouse Jumping Test data for a number of compounds. (DTX 20 at Col. 43:7-63 and Table 2.) As noted above, Otsuka represented to the PTO during prosecution of the '932 patent that the Mouse Jumping Test data demonstrated that the claimed compounds will have antischizophrenic activity. (DTX 471 at 4; Press 130:11-131:25; Marshall 388:5-390:2.)

The '932 patent also contains anti-epinephrine data that shows the compound's propensity to cause the side effect of orthostatic hypotension. This test data shows that when an ethoxy substitution is made on the phenyl ring, it tends to increase alpha-blocking (a lower score here indicates greater blocking activity) and hence increase the liability for causing orthostatic hypotension. (DTX 20 at Col. 43:65-44:28 (and Table 3); Castagnoli 787:14-790:21.) Indeed, the orthostatic hypotension liability potential of the 2-ethoxy phenyl compound was a factor of 2000 times more potent than chlorpromazine a compound known to cause orthostatic hypotension. (Castagnoli 789:7-790:21.) This would have strongly dissuaded a person of ordinary skill in the art from substituting ethoxy molecules on the phenyl ring.

8. *The Wise Poster Discloses Coumarin Compounds as Potential Antischizophrenic Agents.*

While Otsuka was working on carbostyril derivatives, Parke-Davis was working on coumarin derivatives. Carbostyrils and coumarins are very close analogs of each other. (Castagnoli 646:12-16; DTX 274-T at OPC0730595.) The only difference between a carbostyril and a coumarin is that the NH in the carbostyril group is replaced by an O. (Castagnoli 646:3-20.) Coumarin derivatives and carbostyril derivatives are "isosteres" of each other, which means that they have similar electronic configurations. (*Id.* at 646:17-647:17.) They are expected to have similar chemical, spectral, and reactive properties. (*Id.* at 646:3-20.) In fact, coumarin and carbostyril molecules have nearly identical shapes. (*Id.*) At the 1987 annual meeting of the Society of Neurosciences held in Louisiana, Dr. Wise and others from Parke-Davis presented a poster reporting test results on coumarins. (DTX 398.)

a. The Wise Poster Is Prior Art.

Dr. Wise provided deposition testimony, which has been designated in this case, authenticating and explaining the circumstances under which the Wise Poster (DTX 398) was

publicly disclosed and distributed at the 1987 Society for Neurosciences Conference. (Wise Dep. 39:4-17.) Dr. Wise was a group leader of the antipsychotic drug discovery project at Warner-Lambert. (*Id.* at 8:20-9:1.) He testified that he attended the Society for Neurosciences meeting in New Orleans in 1987 as one of eleven thousand attendees. (*Id.* at 10:6-9; 20:13-18.) Dr. Wise has specific recollection of attending that meeting because it was his first trip to New Orleans. (*Id.* at 12:20-13:4.)

Dr. Wise's poster session was a half-day standard poster session related to potential drugs. (*Id.* at 15:17-16:7.) When questioned in his deposition if he could describe what his poster looked like Dr. Wise responded, "[Y]es. I know exactly what [my poster] looked like. It looks exactly like the hand-outs that [Plaintiffs] have today." (*Id.* at 22:20-22.) Dr. Wise recalled that he made his poster with a "photographic process" so that he could have not only a large poster to display but also smaller duplicate copies to use as hand-outs. (*Id.* at 23:1-9.) Dr. Wise testified that he took between "a hundred and two hundred copies" of his poster presentation in handout form to distribute at the presentation and Dr. Wise specifically recalled handing out in excess of a hundred of those poster handouts at the 1987 New Orleans conference. (*Id.* at 33:20-34:6.)

Plaintiff then questioned Dr. Wise if he kept personal files of this 1987 poster presentation. Dr. Wise explained that a scientist's publications were important because publications defined who a scientist was. (*Id.* at 50:9-51:10.) Further, Dr. Wise testified that he "has a file at home that has posters and presentations and patents [he] gave or generated during [his] employment." (*Id.* at 49:9-11.) Dr. Wise's personal file is a file of posters organized in chronological order, and contained a copy of the Wise Poster (DTX 398). (*Id.* at 49:14-19.)

b. Otsuka Considered the Parke-Davis Research on Coumarins to Be Significant and Was Aware of the Wise Poster Prior to October 1988.

Otsuka was aware of the Wise poster prior to October, 1988 (DTX 274-T), but the PTO was not. (Oshiro 1870:8-1872:23.) A September 5, 1988 memo from Mr. Shinichiro Haruki (DTX 274-T), which was copied to one of the inventors of the '528 patent, Dr. Oshiro, discusses the compound disclosed in the Wise Poster by its Parke-Davis compound number, "PD 116795." The commonality of coumarin derivatives and carbostyril derivatives does not end with their structures. The targeted disease in the Wise Poster is schizophrenia. (Castagnoli 652:1-16.) Thus, there was a significant overlap in not only chemistry, but also pharmacology, between the Wise Poster's work on coumarin derivatives and Otsuka's work on carbostyril derivatives. (Castagnoli at 652:17-20; Marshall 326:12-327:5, 353:17-360:24.) The testimony regarding the knowledge of the workers of ordinary skill is confirmed by Otsuka's internal memorandum by S. Haruki, which recognized the structural and pharmacological similarities of Parke-Davis's work on coumarins and Otsuka's own work on carbostyrils. (DTX 274-T (Haruki's Memo); Castagnoli 811-19-815:13; Oshiro 1870:9-1872:18.) Even setting aside the Haruki memorandum, the person of ordinary skill would have paid close attention to the Wise Poster.

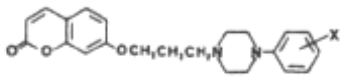
To the extent the commentary in Wise Poster diverges from the actual test results reported, the skilled person would be sophisticated enough to apply the test data in solving a problem presented to him over the commentary, which presented Parke-Davis's opinions, not data, as to how the development of a drug for schizophrenia might be accomplished. (Castagnoli 741:19-746:4; Marshall 352:14-353:6.)

c. The Wise Poster Contains SAR Data That Teaches Butoxy-Linked Compounds Are More Potent Than Propoxy Linked Homologs and That Substituting Chlorine at the 3-Position on the Phenyl Ring Increases Potency over Analogous Methyl and Unsubstituted Compounds.

The Wise Poster contains SAR data for a number of coumarin compounds, which would inform a person of ordinary skill in the art regarding these compounds' structure activity relationships.

The Wise Poster at Table 2, column 2, contains a head-to-head comparison between a propoxy coumarin derivative with a *chlorine* substituted at the 3-position (PD 119,361), a propoxy coumarin derivative with a *methyl* substituted at the 3-position (PD119,519) and a propoxy coumarin derivative with an unsubstituted phenyl ring (PD 116,795). In these tests, the 3-Cl compound is more potent at inhibiting the transmission of dopamine than either the 3-methyl or unsubstituted propoxy compound. (Marshall 362:20-365:14.)

2. INCORPORATION OF SUBSTITUENTS ON THE PHENYL RING RESULTS IN LOSS OF DA AGONIST ACTIVITY



PD	X	[^{3}H]-HALOPERIDOL BINDING % INHIBN (10^{-7}M)	DOPA ACCUMULATION AFTER GBL % DEC (30 mg/kg)	INHIBN LMA IN MICE ED_{50} (mg/kg IP)
116,795	H	85	65	2.6
119,514	4-Cl	24	5	5.6
119,520	4-CH_3	39	0	2.3
119,361	3-Cl	78	32	0.9
119,519	3-CH_3	25	0	8.0
119,581	2-OCH_3	93	0	2.2
119,518	2-CH_3	24	26	2.6

The first test is the haloperidol binding test. This is an *in vitro* test for dopamine receptor affinity that compares the ability of the test compound to displace haloperidol at a dopamine receptor. The ability to inhibit binding of a known antipsychotic drug was known to represent specific binding to the D_2 dopamine receptor, and this test was well-established as highly

predictive of antipsychotic efficacy. (Marshall 351:19-352:22, 2196:1-2197:14; DTX 104; DTX 509; DTX 377-T.) Dr. Roth agreed that this "is a standard test" (Roth 1274:12-15), and that the results here demonstrate that the compounds do specifically bind to the D_2 receptor at the concentration used. (Roth 1275:1-7.) In this test, higher numbers show better binding affinity. (Marshall 2196:1-2197:14; 2200:1-2201:16.)

The second test is the gamma-butyrolactone (GBL) test. The GBL test is an *in vivo* test that selectively measures the compounds' ability to agonize pre-synaptic dopamine receptors (be an autoreceptor agonist). (Marshall 2197:15-25.) In this test, higher numbers show greater pre-synaptic dopamine agonism. No dispute existed that inhibition of DOPA accumulation is highly selective test for dopamine autoreceptor agonism—*i.e.*, activation of the dopamine receptor on the "source" neuron that acts much like a thermostat to control overall levels of dopamine synthesis, release, and thus dopamine neurotransmission. (Marshall 360:22-363:5; Roth 1278:20-1279:3; DTX 104; DTX 377-T.)

The third test is the locomotor activity (LMA) test, which tests the ability of the test compound to inhibit locomotion behavior in mice *in vivo*. (Marshall 329:1-333:6; DTX 736.) The LMA test is an animal behavioral test that is very sensitive to antipsychotic agents. (DTX 736.) Historically, it has been used to assess neuroleptic activity and as a simple and convenient method to identify potential antipsychotic agents. (*Id.*) In this test, lower numbers show better activity in inhibiting dopamine transmission through either the blocking of the post-synaptic D_2 receptor or agonism of the presynaptic D_2 autoreceptor.

Each of these three tests standing alone presents only one measure of a compound's dopaminergic activity. But a person of ordinary skill in the art in 1988 also knew that the principal mechanism of action by which dopamine transmission could be reduced were through

presynaptic D_2 receptor agonism and post-synaptic D_2 antagonism. By reviewing the data from the three tests together, a person of ordinary skill in the art can draw reasonable conclusions about which dopamine mechanism (pre or post) is primarily responsible for the inhibition of locomotor activity. (Marshall 2195:1-2199:23.)

So, it is known that if a compound scored well in the haloperidol binding test, this means that it is targeting and binding well to dopamine D_2 receptors. (Marshall 2196:1-2198:20.) If the compound scores well in the GBL test, that means it is exhibiting dopamine autoreceptor (presynaptic) agonist behavior. If it scores well in the locomotion test, that shows that it also is having the effect on inhibiting the transmission of dopamine. (Marshall 2198:18-2199:24.) Among compounds that bind well, the relative strength of weakness of pre-synaptic agonism in a compound permits a reasonable inference as to whether post-synaptic antagonism is occurring. (Marshall 2198:18-2199:24.)

Both the unsubstituted propoxy compound (PD 116,795) and the 3-Cl substituted compound (PD119,361) score very well in the haloperidol binding test. *Id.* That means that both are binding well at the D_2 receptors. Because they both bind well, the level of D_2 autoreceptor agonism permits an inference as to the level of D_2 post-synaptic antagonism.

In the GBL test, the unsubstituted propoxy compound has a significantly higher score than the otherwise identical 3-Cl compound (65 vs. 32), which indicates the unsubstituted compound is a better presynaptic autoreceptor agonist. (DTX 398; Marshall 363:20-364:22.)

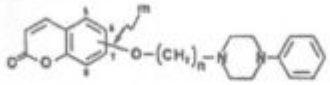
In the locomotion test, the 3-Cl compound is much more potent than the unsubstituted compound (0.9 mg/kg vs. 2.8mg/kg). (DTX 398.) Thus, the 3-Cl compound is more effective at inhibiting the transmission of dopamine than the unsubstituted compound. (Marshall 2195:1-2198:12.) But it is more effective at inhibiting the transmission of dopamine while providing

less D_2 autoreceptor agonism. (Marshall 2198:18-2199:9.) The person of ordinary skill in the art would conclude that the 3-Cl compound obtains more reduction in dopamine transmission by having potent postsynaptic D_2 antagonism—the other mechanism of action that is available. (Marshall 347:8-351:16; 2198:18-2199:24.)

The data from Table 2 of the Wise Poster also provides insight to a person of ordinary skill in the art into the effects of substituting a methyl atom at the 3 position on the phenyl ring for a chlorine atom. (Castagnoli 737:25-739:22.) In each of three different tests for the suppression of dopamine activity, which is an indicator of anti-schizophrenic potential, the 3-Cl compound was more potent than the 3-methyl compound. (DTX 398; Castagnoli 737:25-739:22.) That is a very strong suggestion to substitute chlorine for methyl in order to improve its anti-schizophrenic potency. *Id.*

Table 3 of the Wise Poster provides structure activity relationship data on the effect of linker length on antipsychotic activity. It includes head-to-head test results for the unsubstituted propoxy coumarin derivative (119,981) and the unsubstituted butoxy homolog (PD 199,220) of this compound, together with structure activity data for ethoxy (2-carbon) and pentoxy (5 carbon) homologs in the series. (DTX 398.)

3. A 3- OR 4-CARBON SIDE-CHAIN AND ATTACHMENT OF THE SIDE-CHAIN TO EITHER THE 6- OR 7- POSITION OF THE BENZOPYRANONE ARE NECESSARY FOR DA AGONIST ACTIVITY



PD	m	n	[^{3}H]-HALOPERIDOL BINDING % INHIBN (10^{-7}M)	DOPA ACCUMULATION AFTER GBL % DEC (30 mg/kg)	INHIBN LMA IN MICE ED_{50} (mg/kg IP)
119,981	7	2	28	0	5.1
116,795	7	3	85	65	2.6
119,220	7	4	—	100	0.2
120,078	7	5	85	14	9.4
120,134	6	3	65	69	2.1
119,086	8	3	80	9	4.8

The butoxy compound did even better in both reported animal tests than any other compound. (Marshall 350:4-351:21.) As Dr. Marshall testified:

> Q. And I think it's pretty obvious there are no test data for the haloperidol binding test. Right?
> A. That's correct.
> Q. But there are for the DOPA Accumulation and Inhibition of Locomotion in Mice Test that you previously testified to with respect to Table 2?
> A. Correct. So there are those two pieces of information available. But the authors did not include any information about the tightness of the binding of that particular butoxy compound to the D_2 receptor.
> Q. How about the DOPA Accumulation; what is the significance of that test result?
> A. That test in and of itself would tell you that it is very effective as a dopamine autoreceptor agonist. It inhibited the synthesis of dopamine by 100 percent.
> Q. And how is its potency in the locomotion test in mice in the third column of test results?
> A. It has a potency that's very high, as indicated by the ED50 value of 0.2, which, if I'm not mistaken, is lower, in fact, than any of the values that we saw in Table 2 of column 3 for that test. So very potent.

(Marshall 367:12-368:4.)

Because of the close structural and functional similarity of propoxy coumarin derivatives to propoxy carbostyril derivatives, the Wise poster data comparing propoxy and butoxy coumarin derivatives corroborate the teachings of the Nakagawa Declaration that extending the linker length from propoxy to butoxy would have been expected to increase the antipsychotic potency of the compound. (Castagnoli 645:14-652:20; 674:23-677:18; 681:18-21.) As Dr. Castagnoli testified:

> Q. So bottom line, what would the PHOSITA take away from the Nakagawa declaration and the Wise poster with regard to this issue of the linker length?
> A. Right. So she had three clear teachings: The binding data, the locomotion data, and the jumping data. Maybe we didn't make that clear. That Nakagawa table was

> reporting on Inhibition of Mouse Jumping. She had three clear statements that butoxy is a more potent compound than propoxy in assays which are relevant to the antipsychotic potential of these molecules.

(Castagnoli 677:4-13.)

9. ***Parke-Davis's '456 Patent Discloses a Propoxy Dichloro Coumarin Derivative Version of the Otsuka Propoxy Dichloro Compound Disclosed in SE '945 and DE '105, and Contains Disclosure of Its Use as an Antischizophrenic Agent.***

Parke-Davis also obtained a patent on its coumarin compounds, including some of the compounds of the Wise poster. (DTX 629; Castagnoli 655:14-24.) The patent, U.S. Patent No. 4,701,456, issued October 20, 1987. (DTX 629.) Dr. Wise was one of the inventors on this patent. (*Id.*) This patent included disclosure explaining that these compounds "have been found to have valuable neuroleptic properties, and as such, are useful as antipsychotic agents and as anxiolytic agents." (DTX 629 at Col. 1:24-26; Castagnoli 655:25-656:12.) The patent includes a 2,3 dichloro phenyl propoxy compound that is identical to the carbostyril homolog of aripiprazole disclosed in SE '945 and DE '105 patents except that it has a coumarin rather than a carbostyril skeleton. (DTX 629 at Col. 11:45; Castagnoli 656:17-657:1; 658:14-659:3.) The Haruki memo demonstrates that Otsuka was aware of the '456 patent together with several foreign counterparts of this patent. (DTX 274-T at 2.) A Japanese counterpart of this patent is attached to the Haruki memo. (DTX 274-T at page 3-18.)

F. **FINDINGS OF FACT RELATED TO OBVIOUSNESS-TYPE DOUBLE PATENTING.**

1. ***The Asserted Claims of the '528 Patent Are Not Patentably Distinct from Claim 13 of the '416 Patent Because Aripiprazole Is an Obvious Variant of the Unsubstituted Butoxy Compound.***

Claim 13 of the '416 patent claims the unsubstituted butoxy compound. (DTX 6, Col. 70:62-63.) The structures of aripiprazole and the unsubstituted butoxy are identical except for the substituents at the 2 and 3 positions of the phenyl ring. (Press 100:18-23.) Aripiprazole has

chlorine atoms at those positions, whereas the unsubstituted butoxy has hydrogen atoms. (Press 101:7-21.)

The prior art teaches the unsubstituted butoxy compound's usefulness as an antischizophrenic agent. For example, the '416 patent states that its claimed compounds "are useful for central nervous controlling agents such as . . . antischizophrenia agents." (DTX 6, Col. 3:13-17.) The Nakagawa Declaration reports that the unsubstituted butoxy has "excellent" activity in the Mouse Jumping Test, which per Otsuka's own representations during the prosecution of Otsuka's earlier '932 patent, is a test for determining antischizophrenic activity. (DTX 214 at 14; DTX 471 at 4.)

Accordingly, the only difference between (a) the unsubstituted butoxy compound of claim 13 of the prior '416 patent and (b) claims 12, 17, and 23 of the '528 patent is the chlorine atoms at positions 2 and 3 of the phenyl ring of the aripiprazole molecule. (Press 101:7-21.) The double-patenting analysis, therefore, comes down to the question of whether the person of ordinary skill would have considered substituting chlorine atoms at the 2 and 3 positions of the phenyl group of the unsubstituted butoxy to be an obvious modification.

The evidence at trial established that the substitution of chlorine at the 2 and 3 positions of the phenyl ring of the unsubstituted butoxy would have been a logical, routine, and obvious modification to the person of ordinary skill based on the Nakagawa Declaration and Otsuka's foreign counterparts to the '416 patent. (Press 140:15-141:10.)

As Dr. Press and Dr. Castagnoli testified, the Mouse Jumping Test data from Table 8 of the Nakagawa Declaration would have pointed the person of ordinary skill directly to the addition of chlorine at the 2 and 3 positions on the phenyl ring. (Press 132:1-137:12; 166:24-167:18; Castagnoli 736:12-737:24.) The Nakagawa Declaration provides data showing that a

propoxy compound with chlorine at the 2 position of the phenyl ring and a propoxy compound at the 3 position of the phenyl ring had more antischizophrenic potency than the unsubstituted propoxy compound. (Press 135:20-137:3; Castagnoli 736:12-737:24.) Because propoxy and butoxy compounds are homologs, the person of ordinary skill would have presumed that they behave similarly, and that a butoxy compound with chlorines at the 2 and/or 3 positions would likewise be more potent than the unsubstituted butoxy compound. (Press 137:6-138:4; 166:24-167:15.)

Although the Nakagawa Declaration does not have data on a 2,3-dichloro substituted compound, it would have been obvious for the person of ordinary skill to put chlorine atoms at both the 2 and 3 positions of the phenyl ring. Otsuka's own prior art patent application SE '945 disclosed the 2,3-dichloro propoxy compound, which has chlorines at *both* the 2 and 3 positions of the phenyl ring. (DTX 1159-T at 62; Press 138:8-139:16.) SE '945 additionally discloses that its compounds are useful as antischizophrenic agents. (DTX 1159-T at 5; Press 139:18-24.)

In view of the foregoing, the person of ordinary skill would have considered the substitution of chlorine atoms at the 2 and 3 positions of the phenyl ring of the unsubstituted butoxy to be routine optimization and a logical step in improving antipsychotic potency of the unsubstituted butoxy of claim 13 of the '416 patent. (Press 140:22-10.) Aripiprazole is, therefore, an obvious variant of the unsubstituted butoxy. (Press 127:7-16.) Accordingly, a person of ordinary skill in the art would not have considered claim 12 of the '528 patent, directed to the compound aripiprazole, to be patentably distinct from claim 13 of the '416 patent, directed to the unsubstituted butoxy. (*Id.*) Otsuka offered no evidence at trial that would distinguish claims 12, 17, and 23 from one another with regard to obviousness-type double patenting. Essentially they will stand or fall together. Claim 17 is directed to a pharmaceutical composition

for treating schizophrenia that contains aripiprazole. A person having ordinary skill in the art in possession of the unsubstituted butoxy, having modified it to aripiprazole would have routinely placed the compound into a composition. (Press 141:11-142:5.) Therefore, claim 17 is not patentably distinct from claim 13 of the '416 patent. (*Id.*) Similarly, because claim 23 is directed to a method of treating schizophrenia in a patient using aripiprazole, and the treatment of schizophrenia was the basis for modifying the unsubstituted butoxy, a person of ordinary skill in the art would have also considered claim 23 an obvious variant of claim 13 of the '416 patent. (Press 142:6-19.)

G. FINDINGS OF FACT RELATED TO OBVIOUSNESS UNDER 35 U.S.C. § 103.

1. *Routine Optimization of the Unsubstituted Butoxy Compound Readily Would Have Led a Person of Ordinary Skill in the Art to Aripiprazole.*

Defendants' principal expert on the issues concerning patenting was Dr. Jeffery Press. Dr. Press is an expert in medicinal chemistry and antipsychotic drug discovery with over 25 years of industry experience in pharmaceutical drug research and design. (Press 86:8-12; 77:7-21.) He received his Ph. D. in Organic Chemistry in 1973 from Ohio State University and did postdoctoral research at Harvard University under the direction of Nobel Laureate Robert Burns Woodward. (Press 79:7-20.) Dr. Press is an inventor on more than 50 patents, many of which are related to antischizophrenic drugs, and has authored many articles and book chapters on that topic. (DTX 1441 at 1-10; Press 83:4-84:4.) Notably, Dr. Press discovered the antipsychotic drug olanzapine while working at Lederle Laboratories. (Press 80:11-16.)

The unsubstituted butoxy compound, having no substituents on the phenyl ring, is the parent system for aripiprazole. (Press 100:18-23.) Starting with the unsubstituted butoxy compound, a person of ordinary skill in the art would have been motivated to use chlorine as a

substituent on the phenyl ring based on prior art data from related propoxy compounds. (Press 126:7-127:22; 158:18-159:1; 164:23-166:15; 169:6-171:2.)

The Nakagawa Declaration establishes that propoxy compounds with chlorine at the 2 or 3 positions of the of phenyl ring have more antischizophrenic potency than an unsubstituted propoxy. (Press 135:18-137:14; Castagnoli 737:17-24.) Because the propoxy and butoxy compounds are homologs, the person of ordinary skill would have expected that they behave similarly, and that a butoxy compound with chlorines at the 2 and/or 3 positions would be more potent than the unsubstituted butoxy. (Press 137:4-138:4; 140:22-142:19; 165:21-166:11; 166:24-168:2.) If the person of ordinary skill modified the unsubstituted butoxy by adding chlorines at the 2 and 3 positions, the resulting compound would be aripiprazole. (Press 170:22-171:2.)

a. One of Ordinary Skill in the Art Would Have Selected the Unsubstituted Butoxy as a Lead Compound.

The Nakagawa Declaration provides Mouse Jumping Test data for nine carbostyril derivative compounds, including the unsubstituted butoxy. (DTX 214 at 14; Press 165:5-166:15.) A medicinal chemist would have focused on the 7-linked carbostyril derivatives in the Nakagawa Declaration because the 7-linked compounds OPC-4392 and OPC-4139 were reported to have promising antischizophrenic activity. (Press 164:12-22; Castagnoli 792:3-794:20.) Even though Drs. Roth and Nichols each testified that one of ordinary skill in the art would have chosen the 5-linked compound 44 because it was the most potent, (Roth 1252:3-11; Nichols 1639:22-1640:23), OPC-4392, which had been tested in humans, was a 7-linked compound and a person of ordinary skill would have recognized that changing the position on the core could affect the compound's activity and side effect profile. (Press 160:19-164:22.) Furthermore,

there was nothing in the prior art that would "teach away" from 7-linked compounds because there were no reports of any of them having undesired effects. (Press 166:17-23.)

The declaration shows that compound 41 (the unsubstituted butoxy) is more potent—ED_{50} of 5.5 mg/kg—than compound 6 (the unsubstituted propoxy)—ED_{50} of 9.3 mg/kg. (Press 134:9-135:15; Castagnoli 671:8-672:7.) The data on these compounds allows a "head-to-head" comparison of the propoxy and butoxy linker, which shows that, all else being equal, the butoxy linker was more potent in the test. Because the unsubstituted butoxy is the only butoxy compound in the declaration, its butoxy linker made the compound more potent, and it is "the perfect platform to start structure-activity studies" because it is unsubstituted, a person of ordinary skill in the art would have been motivated to select the unsubstituted butoxy as a lead compound. (Press 164:23-166:15.)

b. A Person of Ordinary Skill in the Art Would Have Been Motivated to Modify the Unsubstituted Butoxy Compound to Make Aripiprazole with a Reasonable Expectation of Success.

A person of ordinary skill in the art, with knowledge of OPC-4392, OPC-4139, the '416 patent, the Nakagawa Declaration, and SE '945 would have been motivated to modify the unsubstituted butoxy compound by dichlorinating the phenyl ring. (Press 164:23-168:5.) In doing so, one would arrive at the 2,3-dichloro butoxy compound, aripiprazole, with a reasonable expectation of success in obtaining an antischizophrenic agent with increased potency. (Press 169:3-170:21.)

Even though the unsubstituted butoxy is the only butoxy-linked compound in Table 8 of the Nakagawa Declaration, the propoxy and butoxy compounds bear such a close structural relationship that chlorine substitution information learned from the propoxy series would have been directly applicable to the butoxy series. (Press 137:15-138:4; 165:5-166:15.) The

Nakagawa Declaration provides data for each of the three chloro substitutions: compound 43 is the 2-chloro propoxy, compound 39 is the 3-chloro propoxy, and compound 16 is the 4-chloro propoxy. (Press 136:8-137:3.) A person of ordinary skill would compare each chloro-substituted compound to the unsubstituted propoxy compound to determine whether the chlorine substitution at each position enhanced or decreased potency. (Press 136:8-137:3; Castagnoli 736:12-737:24.) The 4-chloro substitution on the phenyl ring decreased potency to an ED_{50} of 15.1 mg/kg compared to an ED_{50} of 9.3 mg/kg for the unsubstituted compound, so a person of ordinary skill in the art would not make a compound with a 4-chloro substitution. (Press 136:8-137:3; 165:5-166:15.) The 2- and 3-chloro substituted compounds, having ED_{50} values of 3.3 and 2.5 mg/kg respectively, each significantly increased potency compared to the unsubstituted compound. (Press 136:8-137:3; Castagnoli 737:17-24.)

As Dr. Press explained, medicinal chemists operate on the principle that substituent effects that increase potency will be additive—providing the expectation that increased potency from one enhancement will be further increased by another enhancement. (Press 164:23-168:5.) In other words, the person of ordinary skill would expect that a compound with chlorines at both the 2 and 3 positions would result in a compound with increased antischizophrenic potency, because the prior art taught that both the 2-chloro substituted propoxy compound and the 3-chloro substituted propoxy compound showed increased potency over the unsubstituted propoxy compound. (Press 164:23-168:5; Castagnoli 736:12-737:24; DTX 214 at 14.)

In considering the additive effect of a 2,3-dichloro substitution on the butoxy, a person of ordinary skill in the art would have recognized that Otsuka's own Swedish patent application SE '945 reports that a 2,3-dichloro substitution on the phenyl ring of an unsubstituted propoxy compound led to a compound reported to have antischizophrenic activity. (Press 138:8-139:24;

169:20-171:2; DTX 1159-T at 5 and 60-62.) The person of ordinary skill in the art would have been aware of Otsuka's own prior art patent applications (including DE '105 and SE '945), which disclose the 2,3-dichloro propoxy compound, which has chlorines at *both* the 2 and 3 positions of the phenyl ring. (DTX 248-T at 68; DTX 1159-T at 60-62; Press 138:8-139:24; 169:20-171:2.) Indeed, SE '945 discloses that the 2,3-dichloro propoxy compound had potential use as an anti-schizophrenic agent. (DTX 1159-T at 5; Press 137:4-140:14; 169:20-170:10; Press 137:8-140:14.)

In view of the foregoing, the person of ordinary skill would have regarded the substitution of chlorine atoms at the 2 and 3 positions of the phenyl ring of the unsubstituted butoxy to be a routine and beneficial next step in the development of an antipsychotic drug. The result of this optimization of the unsubstituted butoxy is aripiprazole. From this prior art, a person of ordinary skill in the art would have no difficulty synthesizing aripiprazole. (Press 171:3-171:10.)

> Q. Would a person of ordinary skill in the art have any difficulty making aripiprazole?
> A. Absolutely not.
> Q. Why do you say that?
> A. There's a variety of synthetic methods described in the '416 patent. The starting materials are all available. It's a very simple molecule to construct using routine chemical procedures.

(Press 171:3-171:10.)

Otsuka's experts Dr. Roth and Dr. Nichols both testified concerning the Nakagawa Declaration, but neither directly addressed the structure-activity teachings of Table 8 discussed above. In particular, neither directly rebutted the credible testimony of Dr. Press and Dr. Castagnoli concerning how the person of ordinary skill would interpret the Nakagawa Declaration data on the effect on antischizophrenic potency of (1) the length of the linker and (2)

chlorine substitutions at the 2, 3, and 4 positions of the phenyl ring. In fact, neither of Otsuka's experts provided any testimony at all about the data on the unsubstituted propoxy, the 2-chloro propoxy, the 3-chloro propoxy, and the 4-chloro propoxy compounds contained in Table 8 of the Nakagawa Declaration.

In sum, a person of ordinary skill in the art would have pursued carbostyril derivatives as antischizophrenic agents, selected the unsubstituted butoxy as a lead compound, and been motivated to add a 2,3-dichloro substitution to the phenyl ring to arrive at aripiprazole with a reasonable expectation of success in attaining an improved antischizophrenic agent. (Press 169:18-171:2.) Similarly, a person of ordinary skill would have been motivated to use the modified lead compound and a pharmaceutically acceptable carrier together in a composition to treat schizophrenia. Finally, a person of ordinary skill in the art would have been motivated to treat schizophrenia in a patient using that composition.

2. *Routine Optimization of the 2,3-Dichloro Propoxy Compound Readily Would Have Led a Person of Ordinary Skill in the Art to Aripiprazole.*

Starting where the PTO left off, namely with propoxy dichloro homolog of aripiprazole, but with the benefit of the full scope of the prior art that was not made available to the PTO, it is readily apparent that aripiprazole is an obvious modification of the prior art carbostyril compounds. Adding a link to the linker in the 2,3-dichloro propoxy compound of the SE '945 and DE '105 patents is a modification that chemists call "homologation." (Press 98:7-99:9.) Homologation—the act of making homologs—is a common medicinal chemistry technique for optimizing the properties of a compound and is the "simplest" modification that a chemist would consider. (Castagnoli 667:23-668:11; DTX 1012 at 306; DTX 621 at 337.) It is a strategy that is "as old as organic chemistry." (Castagnoli 670:12-20 (quoting DTX 621 at 337 (Burger's Medicinal Chemistry)).) In this case the difference of exactly one less methylene group in the

linker makes the 2,3-dichloro propoxy the next lower adjacent homolog of aripiprazole. (Press 98:7-9; Goolkasian 505:7-20; 511:1-5.)

Structurally similar compounds, such as homologs, are closely related with similar chemical properties. (Press 99:1-16.) A medicinal chemist would expect homologs to be similar "in the way they are formulated, the way that they're handled, [and] the way that they behave." (*Id.*) In homologation it is expected that the properties of a compound will improve as carbon links are added to a maximum number of carbons and then recede as additional carbons are added in a parabolic relationship. (Castagnoli 735:2-9 ("Well, if I could describe the general picture that one gets with a homologous series, you start at low activity, and you go through a maximum and then come down again. That's this parabolic curve that—plot that was referred to in that paragraph . . . ."); 909:8-24.) Finding the most potent compound is simply a matter of finding the top of the parabola. (*Id.*)

Thus, absent any other teachings it would have at least been obvious to try extending the linker from a propoxy to a butoxy. However, the suggestions in the prior art to extend the linker length, however, goes much further. The prior art Nakagawa Declaration and Wise Poster expressly teach with comparative structure/activity data that a butoxy linker is the best choice. (DTX 214; DTX 398.) The Nakagawa Declaration's Mouse Jumping Test results for the propoxy and butoxy compounds suggest extending the propoxy linker by one link to make it a butoxy. (DTX 214 at 14 (Table 8); Castagnoli 671:18-672:7.) Tests done in the Wise Poster likewise suggest using a butoxy linker. Indeed, those tests teach the superiority of the 4-linked butoxy over not only the 3-linked propoxy but also the 2- and 5-linked versions as well. (DTX 398, Column 2, Table 3; Castagnoli 672:22-677:3; 733:15-735:20.) The butoxy is at the maximum of the parabolic curve for varying the linked length. (Castagnoli 733:15-735:20;

735:5-9 ("Well, if I could describe the general picture that one gets with a homologous series, you start at low activity, and you go through a maximum and then come down again. That's this parabolic curve that—plot that was referred to in that paragraph . . . .").) Further, as Dr. Press explained, "a propoxy to butoxy is a very related compound" and so a medicinal chemist would expect that the effects of chlorine substitution on the propoxy series "would be directly applicable to the butoxy series." (Press 137:15-138:14; 98:7-99:16.) The hypothetical person of ordinary skill, therefore, would have extended the linker to a butoxy with the expectation of obtaining improved potency and, by doing so, would have made aripiprazole.

3. *Routine Optimization of OPC-4392 Readily Would Have Led a Person of Ordinary Skill in the Art to Aripiprazole.*

In 1988, person of ordinary skill in the art looking at the publicly reported results of the clinical trials in humans would have been attracted to OPC-4392 and would have believed that through routine optimizion of that compound she could make an improved anischizophrenic drug compound. (Castagnoli 815:22-816:22.) In developing an antischiozphrenic drug, a person of ordinary skill in the art would seek to make a drug that was good at treating both the positive and negative symptoms of schizophrenia, is non-toxic and had a good side effect profile. (Castagnoli 815:22-816:3.) As noted above, prior art data on OPC-4392 showed that it was very close to meeting this profile. It had great potential as an antischizophrenic drug—it treated negative symptoms, it had low toxicity, it had low EPS side effect liability. (Castagnoli 816:4-22 ("In OPC 4392 [the person of ordinary skill in the art] would have been attracted by this compound – please keep in mind this is a medicinal chemist – because that in humans treated negative symptoms, didn't show toxicity and had a good side effect profile."); 642:12-18; Press 152:10-155:13.) Its only drawback was that it was "not strong" in treating the positive symptoms of schizophrenia. (Castagnoli 642:12-643:12; Press 152:10-153:10.) In other words, it had some

activity, but a person of ordinary skill in the art would have been motivated to make it stronger in treating positive symptoms. (Castagnoli 625:13-626:1; 642:19-644:6; 644:7-23 ("So the [person of ordinary skill in the art] is looking changes which will be simple changes, routine changes, obvious changes that would keep the molecule as close to that – to 4392 as possible, but make a compound with enriched antipsychotic potential."; Press 152:10-153:10.)

The person of ordinary skill in the art had structure activity data in hand at the time that would tell her how to modify the structure of OPC 4392 to improve its potency with the expectation that this would improve its ability to treat positive symptoms. (Castagnoli 658:14-659:3.) For example, as discussed above there was data from the Nakagawa Declaration and Wise poster teaching that by using the basic medicinal chemistry technique of homologation of OPC-4392—growing the linker length from a propoxy linker to a butoxy—a person of ordinary skill in the art would increase the potency of the compound. (Castagnoli 670:11-672:23; 672:24-677:3 678:5-19.) As noted above with respect to the prior art 2,3-dichloro compound, "[t]he simplest change that can be made is . . . to investigate the pharmacology of a homologous series." (DTX 1012 at 306; Castagnoli 668:12-669:7.) Thus, one of the very first things a skilled person would have considered doing with OPC-4392 is changing the length of the linker by adding a link. (Castagnoli 670:11-672:23; 672:24-677:3 678:5-19.)

There were additional teachings from the Nakagawa Declaration that suggested that chlorine substitution on the phenyl ring at the same 2 and 3 positions that OPC-4392 already had methyls present would potentially increase potency of the compound. The skilled person would also have immediately thought of chlorine as a substituent candidate on the phenyl ring. Chlorine is about the same size as methyl and would, therefore, not have been seen as a big structural change. (Castagnoli 739:23-740:16.) There also were teachings from the Wise poster

based on head-to-head comparisons that a chlorine substitution at the 3-position on the phenyl ring would be more potent than a methyl substitution at that position. (Castagnoli 738:2-739:22.)

OPC-4392 was a *double* bonded carbostyril. (Castagnoli 659:8-660:6; 662:2-663:11.) All nine of the compounds in the Nakagawa declaration's report of Mouse Jumping Test results were *single* bonded carbostyrils. (DTX 214 at 14; Castagnoli 651:15-19; 663:1-3.) The coumarins in the 1987 Wise Poster are all *double* bonded. (Castagnoli 651:5-25; 662:23-25.) In view of this mixture of single and double bonded compounds in the prior art, and the absence of any head-to-head studies comparing single and double bonds, the person of ordinary skill in the art would not have picked between these two alternatives. (Castagnoli 662:6-663:11.) The typical research skilled person would instead have made both versions of each compound. (*See id.*) This approach is suggested by the '416 patent's disclosure of about 250 pairs of single and double bonded carbostyril compounds. (Castagnoli 665:4-11.)

Thus, based on prior art data in hand, the person of ordinary skill in the art, by making the simplest, most obvious changes—namely homologation and substituting chlorine for methyl substituents at the 2 and 3 position on the phenyl ring would have expected the potency to increase. This is routine optimization that a person of ordinary skill in the art would have been negligent if she had failed to do. (Castagnoli 809:3-809:24.)

> Q. Professor Castagnoli, in view of all that you've said yesterday and today, do you have an opinion whether the level of skill in the art in 1988 was adequate to develop aripiprazole from the prior art available at that time?
> A. It's my opinion that the level of skill was adequate.
> Q. What would have been your opinion of a research team that had in hand the prior art that you discussed but still did not come up with aripiprazole?
> A. Well, when you consider all of the evidence, I would have -- I would have considered that team negligent.
> Q. Negligent?
> A. Negligent.

> Q. And why is that?
> A. Because the information that was in the prior art clearly documented that by following the basic concept of the dopamine theory of schizophrenia and the evidence in the prior art of how modifications of a drug which had proved in many ways successful in humans in a systematic and rational way, to not have come up with the 4392, to not have come up with the 2,3-dichloro butoxy compound would have meant to me that the team was not competent and would have been negligent.

(Castagnoli 809:3-24.)

In view of the foregoing, the Court credits Professor Castagnoli's testimony that the person of ordinary skill in the art would have gone forward to develop a group of compounds that included (1) changing from a propoxy to a butoxy linker, (2) substituting chlorine for methyl on the phenyl ring, and (3) using single bonds and double bonds in the carbostyril as alternatives. (*See* Castagnoli 791:3-24; 794:1-20; 797:21-798:7;799:8-20; 799:22-800:12;800:24-801:5.) There would have been eight compounds in this group. (Castagnoli 800:24-801:14.) This group would have included the 2,3-dichloro butoxy compound, aripiprazole. (*Id.*)

From making these changes, the person having ordinary skill in the art ("PHOSITA") would have reasonably expected that the modified compounds in this group would have increased potency compared to the prior art and retained a good side effects profile.

> Q. So bottom line, what would the PHOSITA take away from the Nakagawa declaration and the Wise poster with regard to this issue of the linker length?
> A. Right. So she had three clear teachings: The binding data, the locomotion data, and the jumping data. Maybe we didn't make that clear. That Nakagawa table was reporting on Inhibition of Mouse Jumping. She had three clear statements that butoxy is a more potent compound than propoxy in assays which are relevant to the antipsychotic potential of these molecules.
> Q. So what would she do?
> A. She would have done the same thing that she would have done from the information of Nakagawa. She would have

increased the chain length in her series of compounds from propoxy to butoxy.
Q. And what would she expect to get?
A. She would have expected to get just what she's trying to get. That's her expectation. This is supporting her expect -- enhancement in the antipsychotic activity of the resulting molecule.

* * *

Q. What would the PHOSITA in '88 expect from these compounds; what kind of properties?
A. Yes. So she was -- the PHOSITA would expect that these compounds would show enhanced activity going down the list. That is, the compound at the top would be less potent. And when I say "activity," I'm referring to antidopaminergic activity, antipsychotic activity, potential antipsychotic activity.

Replacement of one methyl with chloro or this methyl with chloro would lead to compounds with enhanced activity, and replacement of both methyls with chloro would lead to the most active compound.

* * *

THE WITNESS: May I add one additional comment?
THE COURT: Sure.
THE WITNESS: The additional comment is to appreciate the outstanding exception in terms of human pharmacology that was reported in the clinical studies. That is, what 4392 lacked was this antipsychotic component.

So the PHOSITA is focused on that issue, but she's pretty smart because she doesn't depart from 4392 in any significant way. She stays close to home.
BY MR. CHERRY:
Q. And because she stays close to home, what does she expect with regard to EPS?
A. All right. She expects in staying close to home that those side effects, not only EPS but the others, the hyperprolactinemia and the orthostatic hypotension, which are -- and there's one we haven't talked about, target dyskinesias, which is a very serious outcome of typical neuroleptics -- would not be part of the side effect profile of these compounds. That's her anticipation, her expectation.

* * *

From the changes that she would have made, she would have expected that those new compounds would treat positive symptoms more effectively than 4392. And because the compounds are structurally very similar to 4392, she would

> have expected that those analogs would not have lost the attractive properties of treating negative symptoms, no toxicity, and good side effect profile.

(Castagnoli 677:4-23; 801:14-25; 803:9-804:3; 816:16-22.)

Otsuka contends that the prior art suggests that other changes be made to OPC-4392. The person of ordinary skill in the art could have gone ahead and made at least some of Otsuka's suggested changes as well as the ones discussed above. That would have resulted in a more numerous group of test compounds, but still would have included aripiprazole in the group. For example, Otsuka argues that the prior art suggests changing the attachment point between the carbostyril group and the linker from the 7 position to the 5 position. If that option were added to the group of compounds to be tested by the person of ordinary skill, that would add 8 more compounds to bring the total to 16 compounds. (Castagnoli 804:19-805:23.) Both 8 and 16 are small groups. (*Id.*) Even with the additional compounds it is well within the capability of a person skill in the art to complete a development that inevitably results in aripiprazole. (*Id.*) Otsuka also argues that based on the teachings of the Nakagawa Declaration a person of ordinary skill in the art would have substituted an ethoxy molecule on the phenyl ring. However, as Dr. Castagnoli testified, there was prior art data showing that other ethoxy phenyl carbostyril derivative compounds had a high propensity for causing orthostatic hypotension. (Castagnoli 790:3-21.) Therefore, he would stay away from making such substitutions. (Castagnoli 790:3-21 ("I note, Your Honor, that these carbostyrils differ some to some extent from the propoxy-type carbostyrils. But the message is, don't fool with ethoxy groups because of the liability that this ethoxyphenyl group is going to hurt you.").)

H. SECONDARY CONSIDERATIONS.

1. *Alleged "Unexpected" Superiority.*

a. Increased Antipsychotic Potency Would Have Been Expected Based on the Prior Art.

Otsuka contends that obviousness is negated by alleged "unexpected" superiority of aripiprazole, but Otsuka did not demonstrate unexpected superiority.

The only test data that Otsuka provided was the testing from the Hirose Declaration, submitted to the PTO in 2005, that purported to compare the stereotypy test data of aripiprazole and its prior art 2,3-dichloro propoxy homolog, together with several other pairs of claimed butoxy carbostyril derivative compounds and their corresponding propoxy homologs. The stereotypy test is a subjective not an objective test. (Hirose 1935:21-1936:3; 1936:4-1938:6; Beninger 938:15-940:13; 940:14-943:3; DTX 411; DTX 529; DTX 537.)

As explained in detail herein there were a number of problems with the Hirose testing, including protocols that were not followed and indications of both bias and confound in this data. As explained at trial, Dr. Hirose's purpose in doing these tests was to prove that the butoxies were better than their corresponding propoxy linked analogs. (Hirose 1972:25-1973:6; 1976:5-1980:16.) He was not running experiments to determine results and draw conclusions from the results. He was trying to run experiments that would support a result that he understood was necessary to establish the superiority of the compounds disclosed in the '528 patent. (*Id.* at 1979:15-1980:16.) At trial Otsuka pointed to the Hirose Declaration data showing a 23-fold difference between aripiprazole's potency in the stereotypy test and the potency of the 2,3-dichloro propoxy homolog. (*E.g.*, Roth 1095:25-1096:3.) Otsuka, however, had earlier, contemporaneous stereotypy test data from 1987 that showed the difference was a mere six-fold. (Oshiro 1821:14-1825:8 (explaining that the 2,3-dichloro propoxy had an anti-apomorphine

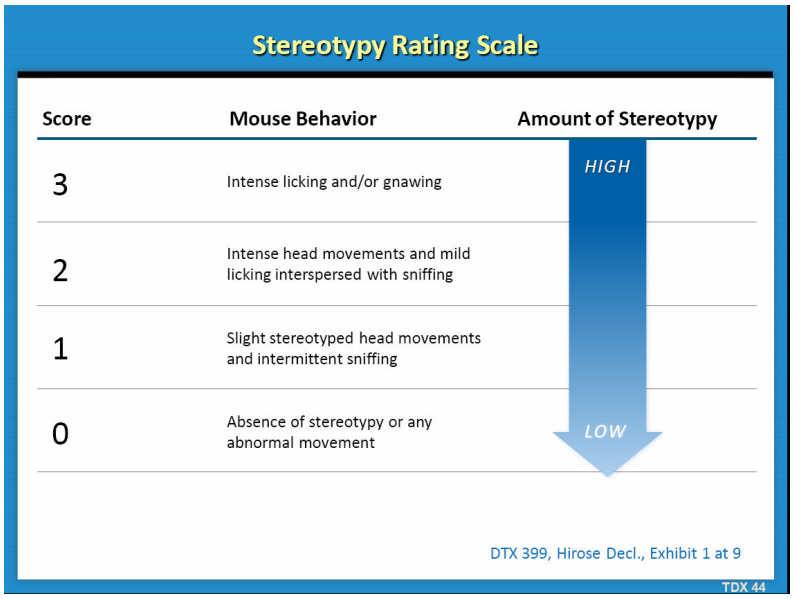
stereotypy ED_{50} value of 2.5 mg/kg and that aripiprazole had an anti-apomorphine stereotypy ED_{50} value of 0.4 mg/kg).) Furthermore, Otsuka's internal documents show that the prior art 2,3-dichloro propoxy compound did better than the known antischizophrenic drug chlorpromazine in both the anti-apomorphine stereotypy and anti-epinephrine lethality tests. (DTX 59-T at OPC0717014; Oshiro 1821:16-25.) The record indicates that the 2,3-dichloro propoxy compound was held back from commercialization by Otsuka, not because of its properties, but rather because it could not be patented due to its disclosure in the prior art SE '945 patent. (Oshiro 1822:9-1827:16.)

On such a record, one cannot assign patentable superiority to aripiprazole. As Dr. Oshiro testified, a difference of a mere six-fold in stereotypy potency was not unexpected and not particularly meaningful. (PTX 37-T; Oshiro 1772:12-1773:3 (explaining that Otsuka "did not find a considerable increase in the activity" between OPC-4392 and butoxy analog which showed only a six-fold difference in potency); Oshiro 1844:18-1845:8 (comparing the anti-apomorphine stereotypy ED_{50} value of 1.4 mg/kg for OPC-14565, the butoxy analog of OPC-4392, with the anti-apomorphine stereotypy ED_{50} value of 9.3 mg/kg for OPC-4392).)

As explained in the legal conclusions Section IV(D)(4)(a), in assessing alleged unexpected results, one must compare aripiprazole with what properties were expected from the teachings in the prior art. As discussed above, one would have expected improved potency in switching from a propoxy linker to a butoxy linker and in switching to a chlorine substituent on the phenyl ring. Thus, aripiprazole's possession of an improved potency in the stereotypy test would not qualify as evidence of "unexpected superiority" because that would have been expected, not unexpected.

b. The Stereotypy Data Supporting Otsuka's Alleged Unexpected Results Were Biased and Confounded.

The PTO relied on the stereotypy data in the Hirose Declaration as the basis for allowing the '528 patent to issue from the reexamination. However, this data was unreliable because it was the result of test protocols, different from those disclosed to the PTO, that were susceptible to confound and bias. First, the methodology Otsuka actually used created a confound because two observers scored the test mice in a manner that made it impossible to know whether the differences in scores were due to the observer or the test compound—*i.e.*, one observer scored all of the aripiprazole test mice and the other scored all of the 2,3-dichloro propoxy test mice. (*See* Beninger 937:11-14, 938:1-10; Hirose 1986:8-14.) The second issue is possible bias because the observers scoring the mice were not blinded to the identity of the compounds being tested. In other words, not only did the Otsuka employees performing the test start with the premise that the claimed compounds need to appear superior to the prior art compounds, they also knew which compounds the mice they were scoring had received. (Beninger 929:11-21; 956:7-11.) The problems with the methodology of Dr. Hirose's experiment are rooted in the fact that the anti-apomorphine induced stereotypy test is scored using a subjective scale. (Beninger 938:15-939:20; 940:10-942:18; DTX 537; DTX 411; DTX 529.) The anti-apomorphine stereotypy test is a subjective test because the observer must make an individual judgment as to which level on a scoring scale an animal's behavior falls into. (Beninger 938:15-939:20.) The scoring scale used for the testing in the Hirose Declaration is illustrated as follows.



(TDX 44 (citing DTX 399, Ex. 1 at 9).)

The scale is inherently subjective because it requires the observer to not only judge *whether* an animal exhibits stereotyped behaviors, but also to assess the *intensity* of the behaviors being observed. (DTX 411 at 253; Beninger 939:18-20.) For example, the observer using this scale must judge "mild" versus "intense" licking to choose between a rating of 2 and a rating of 3. (Beninger 938:15-939:20.) Similarly, the observer must make a distinction between "intermittent sniffing" and "sniffing" to distinguish between a rating of 1 and a rating of 2. (Beninger 938:15-939:20.)

Defendants' expert Dr. Beninger testified regarding the bias and confound issues and how Otsuka's testing protocol rendered the test data generated of questionable reliability. (Benninger 940:20-943:7.) Dr. Beninger is an expert in behavioral pharmacology and has extensively studied potential antipsychotic drugs and the dopamine system. Dr. Beninger is very experienced in using animal models that correlate with antischizophrenic activity in humans for a number of years, and maintains an animal laboratory with approximately 150 rats to conduct his research on dopamine receptor blockers and antipsychotics. (Beninger 917:16-918:4, 920:4-7;

see Beninger 924:21-925:9.) He has personally performed stereotypy testing and has overseen such testing in his lab. (Beninger 920:18-921:23.) Dr. Beninger testified that the use of a subjective scale in scoring stereotyped behavior is a particular concern in the field. (Beninger 940:10-16.) He also highlighted several publications that have noted that the use of a subjective scoring scale—even among experienced observers—may lead to confusion, difficulty in matching behaviors of animals to scores, and, consequently, uncertainty and variability in scores. (Beninger 940:18-942:18.)

Otsuka has provided no credible evidence to the contrary. Furthermore, Dr. Roth, admitted that while he believes whether the stereotypy test is subjective is a "matter of semantics" (Roth 1116:8), the test may well be subjective in this type of research. (Roth 1116:7-22.) The subjective nature of stereotypy rating scales was recognized in the art and Otsuka has provided no credible evidence to the contrary. (Beninger 940:10-942:18; DTX 537; DTX 411; DTX 529.)

As Dr. Beninger explained, "[a] confound in an experiment occurs when two variables change at the same time, making it not possible to ascertain which of the two variables is responsible for an observed effect." (Beninger 930:5-9.) Here, the two variables that changed at the same time were the observer and the compound. That is, for each claimed compound and prior art compound pair, Dr. Hirose scored all the mice for one compound and Dr. Kikuchi scored all the mice for the other compound. For example, Dr. Hirose scored the anti-stereotypy effects of aripiprazole (compound 1) and Dr. Kikuchi scored the anti-stereotypy effects of the 2,3-dichloro propoxy (compound A). (*See* Beninger 937:11-14; 938:1-10; Hirose 1986:8-14.) It cannot be determined whether the difference in ED_{50} values between compound 1 and compound A is due to a difference in the observers' subjective scoring or due to a difference in the

compounds. (Beninger 938:1-14.) In other words, it cannot be determined whether the difference in ED_{50} values is due to any difference in potency between compounds 1 and A, or due to a difference in Dr. Hirose's and Dr. Kikuchi's scoring interpretations.

Additionally, a bias was present when Dr. Hirose and Dr. Kikuchi scored the mice behaviors because they knew the identity of the compounds being tested and knew which compounds should have superior results. Dr. Beninger explained that "[e]xperimenter bias can occur when . . . somebody doing the rating or scoring has an expectation of the outcome." (Beninger 946:23-947:4.) This expectation "can consciously or unconsciously influence the decisions made by an individual." (*Id.*) Here, Drs. Hirose and Kikuchi not only had an expectation of the outcome, they knew what outcome was necessary to overcome the PTO's rejection. Further, Drs. Hirose and Kikuchi were not blinded to the identity of the test compounds, and therefore knew which mice were in the aripiprazole test group and which mice were in the prior art 2,3-dichloro propoxy compound test group. (Thisted 1471:2-4; Hirose 1986:8-14.)

The potential for bias is even greater when dealing with a test, such as this, that involves scoring of minute differences in behavior. For instance, when scoring the anti-stereotypy effects of aripiprazole, Dr. Hirose may have more readily chosen a score of 1 (a better score) indicating "intermittent sniffing" over a score of 2 (a worse score) indicating "mild licking interspersed with sniffing" because the purpose of the test was for aripiprazole to be "superior" compound. (Beninger 955:2-10.) Likewise, when scoring the anti-stereotypy effects of the prior art 2,3-dichloro propoxy, Dr. Kikuchi may have more readily chosen a score of 2 (a worse score) over a score of 1 (a better score) because the purpose of the test would be for the prior art compounds to be less superior compounds. (*Id.*) Thus, whether conscious or unconscious, a bias was present

when Dr. Hirose and Dr. Kikuchi scored stereotyped behavior because the expectation of the claimed compounds performing better could result in shifting between scores at the transitions—*e.g.*, a score of 2 to a score of 1. (Beninger 947:25-13; 955:2-10.) This bias calls in to question conclusions regarding the differences in the reported ED_{50} values, and undercuts Dr. Hirose's conclusion that the claimed compounds have greater antipsychotic potency. (Beninger 956:7-11; DTX 399 ¶ 15.)

The confound and bias is inherent in the methodology used for the Hirose Declaration. A statistical analysis cannot eliminate the concerns regarding confound and bias. (Beninger 946:2-7; 955:13-20.) The statistical analysis by Otsuka's expert, Dr. Thisted, who admittedly had never assessed stereotypy test data or examined control dosages to determine whether or not there was bias before this case, only included the stereotypy scores from the control mice—namely, the mice that received no test drug. Dr. Thisted's analysis did not include a comparison of the stereotypy scores from the mice that actually received the test compounds. (Thisted 1499:20-1500:3; 1500:3-1501:24; Beninger 946:2-11; Roth 1305:16-1306:7.) Even if a statistical analysis indicated that Drs. Hirose and Kikuchi did not differ in their scoring of the control mice, that does not resolve whether Drs. Hirose and Kikuchi differed in their scoring of mice that actually received test compounds. (Beninger 943:25-945:6; 946:2-17; *see also* 955:11-20.)

Otsuka contends that even though the observers were not blinded to the identity of the test compound, any potential bias was eliminated because the observers were blinded to the dose of the test compound the mice received. Blinding the observers to the dose, however, did not eliminate the potential bias. (Beninger 955:2-20.) Dr. Roth opined that the protocol was a "perfectly acceptable" way to do the experiment. (Roth 1107:8-1108:25.) However, this

methodology still allows for potential bias because the observers' knowledge about the identity of the test compound could still affect their judgments and cause shifting between scores at the transitions, and it would have been easy to avoid this flaw. (Beninger 955:2-20.) Neither Dr. Roth's nor Dr. Thisted's analysis of the data could eliminate concern over potential "systematic bias in the data" because systematic bias could affect the entire curve and the control dose would not reveal the effects of bias at the scoring transitions. (*Id.*; Roth 1115:22-25; Thisted 1462:12-1463:13.) Therefore, the potential for bias makes it impossible to draw any reliable conclusions from anti-apomorphine induced stereotypy the results in the Hirose declaration. (Beninger 957:7-11.) Thus, the Hirose declaration stereotypy results cannot prove that aripiprazole is unexpectedly superior to the prior art 2,3-dichloro propoxy compound in antischizophrenic potency. (*See* DTX 399 ¶ 15.)

c. Otsuka Also Failed to Make Any Other Presentations of Actual Difference from the Closest Prior Art.

Otsuka's other evidence of alleged unexpected results fail to demonstrate actual differences from the closest prior art. For example, Dr. Roth's "Heat Map" compares the receptor activity of aripiprazole to several other marketed antipsychotic drugs such as risperidone and clozapine. This chart, however, never addressed the receptor profile of the prior art carbostyril derivatives such as the 2,3-dichloro propoxy compound, the unsubstituted butoxy compound, or OPC-4392. Otsuka's arguments about aripiprazole being approved for major depressive disorders, for certain aspects of Bipolar I Disorder, and for treatment of irritability associated with autistic disorder in pediatric patients (Jarosz 2006:15-2007:6) similarly fail to compare the *closest prior art* carbostyril derivative compounds. The other close prior art carbostyril derivative compounds may well have such properties. For example, the '416 patent states that its compounds are useful as, *inter alia*, "antimanic-depressive agents" (*i.e.*, useful in

treating bipolar disorder). (DTX 6 at 3:17-18; Roth 1220:13-1221:9; Jarosz 2110:18-2112:2.) Thus, aripiprazole's approval for these other indications is hardly unexpected. Otsuka's proofs are flawed because they do not make the relevant comparisons of aripiprazole to the relevant prior art carbostyril derivatives to show that they actually have different properties.

d. Otsuka's Blocking Patents Sever Any Nexus Between the '528 Patent Claims and Unexpected Properties.

The relevance of evidence of alleged unexpected superiority to an obviousness analysis is based on the inference that "if others in the art could have come up with a product" having the allegedly superior property, "they certainly would have done so." *In re D'Ancicco*, 439 F.2d 1244, 1248 (C.C.P.A. 1971). That inference cannot be drawn here because Otsuka's extensive patent position discouraged others from working in the carbostyril derivative field. (Press 116:14-117:5; 173:21-174:5; 174:11-23; 190:8-20; Nichols 1710:18-1714:10.)

Otsuka's several prior art patents on carbostyril derivatives laid claim to an enormous number of compounds. (DTX 6; DTX 20; DTX 248-T; DTX 1159-T.) The '416 patent alone covered at least nine trillion compounds. (Nichols 1624:8-12, 1716:17-1717:2.) The '416 patent therefore removed that entire class of compounds from the public's hands. (Press 116:14-117:5; Roth 1241:9-22; Nichols 1624:8-1626:3.) This eliminated any incentive for persons in the field of antischizophrenic drug research to pursue carbostyril compounds. Dr. Press explained the situation as follows:

> [P]harmaceutical companies do this because they hope to make a drug out of it to make money.
>
> If they have their scientific staff looking at a drug or drug candidate that's owned by somebody else, they're not expending their resources very well.
>
> And so people in another company that don't own the compound wouldn't pursue those compounds because they know they wouldn't have a benefit to their company at the end.

(Press 174:16-23); *accord Brenner v. Manson*, 383 U.S. 519, 534 (1966) (footnote omitted) (Broad patents have the "power to block off whole areas of scientific development."); *id.* ("To the extent that the patentee has power to enforce his patent, there is little incentive for others to undertake a search for uses" of what is precluded by that patent.); *Princo Corp. v. Int'l Trade Comm'n*, No. 2007-1386, 2010 WL 3385953, at *27 (Fed. Cir. Aug. 30, 2010) (Dyk, J., dissenting) ("The mere threat of an infringement suit is typically sufficient to prevent a potential competitor from devoting the resources necessary to develop an alternative technology; the technology is thus suppressed at the outset.").

Because Otsuka's patents covered not only aripiprazole but also, according to Otsuka's witnesses covered billions or trillions of other carbostyril compounds, the most likely inference is that others stayed away from carbostyrils out of fearful respect for Otsuka's prior art patent portfolio. For example, Dr. Press, speaking from personal experience, testified that when Lederle was faced with Eli Lilly's prior patent position on the drug olanzapine, Lederle was left "[w]ithout the ability to protect [its] work" and within a short time its "antipsychotic program was shut down." (Press 80:11-81:5, 190:8-20.) Prof. Nichols likewise testified that a pharmaceutical firm would likely not pursue a lead compound once it was learned that it was covered by someone else's patent. (Nichols 1712:17-1714:10.) In this case, Otsuka's pre-existing dominant patent position in carbostyrils undermines any inference that technical difficulties were the reason for why others did not develop aripiprazole or another carbostyril with the superiority alleged by Otsuka.

This analysis is not changed by the fact that some generic pharmaceutical firms *subsequently* sought *improvement* patents. Aripiprazole was approved by the FDA on November 15, 2002. (Jarosz 2112:3-7.) It was not until April 22, 2004, that the earliest of these other

patent applications was filed. (PTX 659 (claiming a priority date of April 25, 2003); Press 317:18-24.) The most natural inference from this sequence of events is that aripiprazole's FDA approval triggered an interest in obtaining patents relating to improvements such as how to better manufacture the drug or how to better formulate it for better reception in the body. These later improvement efforts are not comparable to developing the new compound itself back in 1988. These later improvement patents in no way suggest that a large pharmaceutical firm would commit itself to developing a new drug knowing that a competitor's patents not only blocked sales but also interfered with getting one's own patent exclusivity. (Press 80:11-81:5; 190:8-20.) This is illustrated by Dr. Press's experience at Lederle where the olanzapine project was abandoned once it was learned that Eli Lilly had the dominant patent position. (Press 80:11-81:5; 190:8-20.) It is also corroborated by Otsuka's own internal policy of not pursuing the development of compounds that cannot be patented because they are disclosed in prior art patents. (Oshiro 1826:20-1827:16.)

2. ***Alleged Copying.***

Otsuka argues "copying" based on defendant's ANDAs seeking to market generic forms of aripiprazole. When a patentee asserts its patent is nonobvious because it was "copied" by a competitor, the inference that it seeks to draw is that the technical challenges were so great that success was beyond the reach of those of ordinary skill in the art. The requisite inference, however, simply cannot be drawn here because Defendants' alleged "copying" behavior is a result of Hatch-Waxman Act incentives, not a failure to overcome some technical hurdle.

3. ***Alleged Commercial Success.***

Otsuka's blocking '416 patent also undercuts any inference of nonobviousness based on alleged commercial success of aripiprazole. Otsuka's prior patents covered aripiprazole, plus a large number of other carbostyril compounds. The very purpose of these patents was to

discourage competitors. One is entitled to infer that these patents achieved their intended purpose of keeping competitors off Otsuka's carbostyril reservation. There is no basis for inferring that market forces drove others to try and then fail to develop a commercial aripiprazole product, which is the inference on which reliance upon commercial success would be based. Subsequent improvement patent activity by generic firms does not alter this conclusion because it does not relate to how a competing large pharmaceutical firm would have earlier gone about developing a new antischizophrenic compound in the first place.

Despite there being more than one patent that covered aripiprazole Otsuka presented no evidence attempting to ascertain to what extent the commercial success of aripiprazole is due to the benefits of the prior art '416 patent as distinct from the '528 patent. (Jarosz 2106:9-13; 2106:14-15; 2113:15-20; 2116:6-12; 2116:21-2117:2.)

Abilify® was the subject of "a very substantial advertising and promotional campaign," and the promotional spending was large relative to other atypical antipsychotics. (Jarosz 2134:23-2135:6.) According to industry accounts from credible sources (Medical marketing and Media, Pharmalive.com and Consumer Reports), Otsuka and BMS spent $150 million on direct-to-consumer advertising of Abilify® in the first nine months of 2009. (Jarosz 2138:4-7.) This represented a 75% increase in direct-to-consumer advertising by Otsuka and BMS compared to the same expenditures in the first nine months of 2008. (Jarosz 2138:8-11.) In 2009, Otsuka and BMS spent $202.2 million on direct-to-consumer advertising of Abilify®. (Jarosz 2146:25-2147:3.)

Otsuka's commercial success evidence between November 2002 and the end of 2005 is tainted by sales of aripiprazole arising from Otsuka's and BMS's unlawful promotion and sale for uses not approved by the FDA. According to allegations brought by the U.S. Department of

Justice and the United States Attorney for the District of Massachusetts, beginning in November 2002 through the end of 2005, both Otsuka and BMS "knowingly promoted the sale and use of Abilify®, an atypical antipsychotic drug, for pediatric use and to treat dementia-related psychosis, both "off-label" uses. (DTX 1461, pp. 1-2; Jarosz 2152:10-19.) During this time period, the FDA had "not approved Abilify® for children and adolescents or for geriatric patients suffering from dementia-related psychosis." (*Id.*; *see* DTX 1462; Jarosz 2152:20-2153:2; 2151:18-23.) Otsuka and its U.S. sales partner BMS paid fines for illegal sales practices involving Abilify®. (Jarosz 2151:18-2156:9; DTX 1461; DTX 1462.) Mr. Jarosz's commercial success analysis does not attempt to remove those sales relating to the "off-label" use of aripiprazole between November 2002 and December 2005. (Jarosz 2150:20-2151:1.)

Accordingly, Otsuka's evidence fails to support an inference of unobviousness.

4. *Alleged Long-Felt Need and Failure of Others.*

Otsuka argues that the development of aripiprazole solved a long-felt need for a safe and effective antipsychotic for the treatment of schizophrenia with reduced side effects. But another atypical antipschotic drug, Risperidone, already was successfully treating patients for schizophrenia in human clinical trials more than a year before the application for the '528 patent was even filed. (DTX 990 at 238.) Furthermore, aripiprazole was not the first atypical antipsychotic to receive FDA approval for use in treating schizophrenia—it was actually the sixth atypical antischizophrenic drug to enter the United States market. (Jarosz 2090:15-20.) Five other FDA approved atypical antischizophrenics preceded aripiprazole to market demonstrating that "different manufacturers with different drugs [had] succeeded in this business." (Jarosz 2062:3-4.) They are clozapine (1990), risperidone (1994), olanzapine (1996), quetiapine (1997), and ziprasidone (2001). (*Id.*) After aripiprazole was approved, three additional atypical antipsychotics received FDA approval for treating schizophrenia—

paliperidone (2007), iloperidone (2009), and asenapine (2009). (Jarosz 2062:4-6.) This undercuts any inference that others must have tried and failed to bring an atypical antischizophrenic drug to market. Instead, it demonstrates that the level of skill in the art was high enough to overcome any technical hurdles to successfully bringing an atypical antischizophrenic to market.

With respect to prior carbostyril compounds, others seeking to address the long-felt need would have been discouraged by Otsuka's blocking patent position. (Press 116:14-117:5; 173:21-174:5; 174:11-23; 190:8-20; Nichols 1710:18-1714:10.)

Development by others was further restricted by the regulatory framework of the Hatch-Waxman Act and the high barriers to entry for parties seeking to market a new chemical entity. A scientist cannot simply develop a new drug treatment for schizophrenia and start selling it. Rather, the scientist must have the immense resources necessary for animal and then human testing, as well as an extensive marketing and sales force to satisfy the regulatory hurdles imposed by the FDA and then get the drug to market. Thus, the explanation for why others did not develop aripiprazole through the optimization of prior art carbostyril compounds (as Otsuka did) or conduct research into the potential use of carbostyril compounds is not the alleged nonobviousness of aripiprazole, but rather that Otsuka had already used patents to block out all others from pursuing this route and that the regulatory system erected barriers to entry faced by others seeking to market such a compound. (Press 116:14-117:5; 173:21-174:5; 174:11-23; 190:8-20; Nichols 1710:18-1714:10.)

Also cutting against a finding of longfelt need is that there were only a few months between the public disclosure of a critical piece of prior art, namely, the Nakagawa declaration,

that became available upon the issuance of the '416 patent in March, 1988, and Otsuka's October 1988 Japanese filing date for the '528 patent. (DTX 214; DTX 498.)

5. *Alleged Industry Acclaim.*

Otsuka also relies on industry acclaim, such as the 2006 Prix Galien award for the development of aripiprazole. This and the other awards were presumably for the entire research effort made by Otsuka. There is no evidence that the awarding authorities made any attempt to sort out the last increment of development that took the program from the portions of Otsuka's own work that is citable as prior art, such as OPC-4392 and the Nakagawa declaration, to aripiprazole.

I. FINDINGS OF FACT RELATED TO INEQUITABLE CONDUCT.

1. *Summary of Reexamination Proceedings.*

On August 11, 2004, Otsuka submitted the '528 patent to the PTO for reexamination. (DTX 121 at 00004-25.) Charles E. Van Horn, a partner at Finnegan, Henderson, Farabow, Garrett & Dunner, LLP, prepared, submitted, and prosecuted the reexamination request for the '528 patent on behalf of Otsuka. (Van Horn Dep. 11:20-21; 28:8-16.) Dr. Oshiro, a named inventor on both the '416 and '528 patents, was intimately involved with the reexamination. (DTX 6; DTX 498.) At the time of the reexamination proceedings, Dr. Oshiro was serving as an advisor to Otsuka's intellectual property department. (Oshiro 1793:17-23.) Dr. Oshiro attended at least ten meetings with Finnegan Henderson and other Otsuka personnel concerning the reexamination. (Hirose 1914:9-21; 1916:20-23; 1917:4-10; 1917:23-1918:3; 1972:4-17; *see* Van Horn Dep. 32:4-33:2.) Moreover, as Otsuka's privilege log indicates, Dr. Oshiro had over 300 communications with the Otsuka intellectual property department and/or Otsuka's counsel Finnegan Henderson related to the reexamination proceedings. (DTX 61-A; *see* Oshiro 1877:15-1880:18; Hirose 1915:3-19.)

Otsuka's reexamination request stated that the '416 patent, among other Otsuka patents and publications, raised a "substantial new question of patentability." (DTX 121 at 00004-05; Goolkasian 490:12-19; 559:8-560:8.) As Otsuka explained to the PTO, the compounds of the '416 patent are "disclosed as having central nervous controlling effects" and "it can be argued that the use of the described compounds as antischizophrenia agents is specifically contemplated." (DTX 121 at 00007.)

During the '528 patent reexamination, the examiner repeatedly rejected all the '528 patent claims for obviousness based on Otsuka's own prior art patent documents. (DTX 121 at 01144-51, 01235-51, 1320-34) The examiner found that "it would have been obvious for one of skill in the art to make slight modifications to obtain the compounds of the invention." (DTX 121 at 01235-51, 01328) In particular, the examiner rejected the claims of the '528 patent over five exemplary carbostyril derivatives disclosed in prior art references, including the '416 patent and its foreign counterpart DE '105. (Oshiro 1880:20-1881:23; DTX 121 at 01241-42.) Three of those five exemplary carbostyril derivatives were the unsubstituted butoxy, the 5-linked 2-ethoxy propoxy, and the 7-linked 2-methoxy propoxy. (Oshiro 1880:20-1881:23; DTX 121 at 01241-42.)

In a May 16, 2005 Amendment, Otsuka represented to the examiner that "there is no evidence that the five exemplary carbostyril derivatives identified by the Examiner have . . . the recited property of treating schizophrenia." (DTX 459 at OPC0001554 (DTX 121 at 01274); Goolkasian 500:10-501:3.) Otsuka's arguments failed to change the examiner's mind, and a final rejection was issued. In the final rejection, the examiner again set out the five exemplary compounds from the '416 patent, which, according to the examiner, "teaches the compounds

with the same genus" to be useful in "central nervous system disorders in which anti schizophrenia [sic] is also disclosed." (DTX 121 at 01324-27; Goolkasian 502:15-504:19.)

In response to the final rejection, Otsuka filed a request for reconsideration in which it again represented to the examiner that "there is no prior art evidence that the five exemplary carbostyril derivatives identified by the Examiner have . . . the recited property of treating schizophrenia." (DTX 4 at OPC0001628 (DTX 121 at 01348); Press 179:20-182:9; Goolkasian 509:23-510:9.)

Together with the request for reconsideration, Otsuka submitted a declaration by Otsuka employee Dr. Hirose. The Hirose Declaration presented animal test results that purported to show "unexpected" superiority of the claimed compounds over Otsuka's prior art carbostyril derivatives based on the switch from a "propoxy" linker disclosed in the prior art to a "butoxy" linker. (DTX 399 ¶ 6.) The two tests used in the Hirose Declaration were the anti-apomorphine stereotypy test and the anti-epinephrine lethality test.

Dr. Hirose and his colleague Dr. Kikuchi tested four pairs of compounds that differed from each other only in the length of the linker. One pair of compounds tested by Drs. Hirose and Kikuchi was aripiprazole (compound 1) and Otsuka's prior art 2,3-dichloro propoxy compound (compound A). (DTX 399 ¶ 14 (DTX 121 at 01368-69.) The only difference between these two compounds is that aripiprazole has a butoxy linker and the 2,3-dichloro propoxy has a propoxy linker. The Hirose Declaration reports that the ED_{50} of aripiprazole in the anti-apomorphine steretopy test to be 0.28 mg/kg and the ED_{50} of the 2,3-dichloro propoxy to be 6.47 mg/kg. (DTX 399, Table 1 (DTX 121 at 01370-71).) Dr. Hirose concluded in his declaration that aripiprazole and the other butoxy compounds were unexpectedly superior to the

2,3-dichloro propoxy and the other propoxy compounds. (DTX 399 ¶¶ 15, 17 (DTX 121 at 01373-74.)

Based on the test results in the Hirose Declaration, Otsuka argued that the change from the propoxy linker to the butoxy linker resulted in an "unexpected" improvement. (DTX 4 at OPC0001635-43 (DTX 121 at 01355-63); *see* Goolkasian 510:10-512:9.) The reexamination examiner's statement of "Reasons for Patentability/Confirmation" shows that she was persuaded by Otsuka's assertion of "unexpected" superiority based on the change from a propoxy linker to a butoxy linker:

> The compounds [of] claims 1-21 are found to be allowable since applicants have compared their compounds with the closest prior art. The ones with just one difference in the linker chain, propyloxy [a/k/a propoxy] to a butoxy chanin [sic, chain] shows a clear unexpected result in the ED50 values.

(DTX 121 at 01412; Goolkasian 527:12-20.)

2. *Otsuka Withheld Data Showing That the Increase in Potency Between the Butoxy Compounds and the Propoxy Compounds Was Not Unexpected.*

a. Otsuka Withheld the Nakagawa Declaration Data.

Otsuka never told the PTO about the data in the Nakagawa Declaration, which, as discussed above, demonstrated that the unsubstituted butoxy had more antischizophrenic potency than the unsubstituted propoxy compound. (*See* DTX 214; Press 138:5-7; Goolkasian 511:18-512:11.) The Nakagawa Declaration data directly contradicted Otsuka's argument that increased antischizophrenic potency in a butoxy compound as compared to a propoxy compound would be unexpected.

Dr. Oshiro admitted at trial that he knew about Otsuka's Mouse Jumping data on the unsubstituted butoxy. (Oshiro 1867:2-6.) The only internal Otsuka data containing the ED_{50} value for OPC-4152 (the unsubstituted butoxy) in the Mouse Jumping Test agreed with the 5.5

mg/kg ED_{50} value found in the Nakagawa Declaration. (Oshiro 1869:5-17; *see* DTX 208-T at OPC0616309; Oshiro 1868:10-19; 1868:21-23; *see also* DTX 214 at 5, 14.) Dr. Nakagawa was Dr. Oshiro's boss in the synthesis department at Otsuka. (Oshiro 1860:25-1861:5.) Dr. Nakagawa testified in designated deposition testimony that Dr. Oshiro likely worked on the data underlying the Nakagawa Declaration. (Nakagawa Dep. 140:21-25.)

Defendants' expert John T. Goolkasian testified at trial that a reasonable examiner would have found the information in the Nakagawa Declaration to be material. (Goolkasian 516:14-517:13; *see* Goolkasian 511:18-512:11.) Mr. Goolkasian worked at the Patent Office as both a primary and supervisory patent examiner, and examined over 1500 patent applications. (Goolkasian 456:17-457:1.) Mr. Goolkasian also worked as an *inter partes* and *ex parte* examiner for the Office of the Assistant Commissioner in the PTO where he investigated allegations of inequitable conduct. (Goolkasian 452:16-453:2.) In 1983, he was appointed to the Board of Patent Appeals and Interferences, where he served for over ten years. (Goolkasian 453:3-453:5; 457:2-4.) Mr. Goolkasian has a bachelor's degree in chemical engineering from Northeastern University and a law degree from Georgetown University. (Goolkasian 450:21-451:1.)

b. Otsuka Withheld Internal Anti-Apomorphine Stereotypy Data on Aripiprazole and the 2,3-Dichloro Propoxy That Were Inconsistent with the Hirose Declaration.

As set forth above, Otsuka represented to the PTO in the Hirose Declaration that the ED_{50} of aripiprazole in the anti-apomorphine stereotypy test was 0.28 mg/kg and the ED_{50} of the 2,3-dichloro propoxy was 6.47 mg/kg. As Otsuka's expert Dr. Roth pointed out at trial, these results indicated to the PTO that aripiprazole was 23 times more potent than the 2,3 dichloro propoxy. Otsuka's internal data revealed, however, that there was actually a much smaller difference in potency between these compounds.

Otsuka's internal data from anti-apomorphine stereotypy tests it performed outside the context of the patent prosecution showed that aripiprazole actually had an ED_{50} of 0.4 mg/kg and the 2,3-dichloro propoxy had an ED_{50} value of 2.5 mg/kg. (DTX 59-T at OPC0717014; Oshiro 1821:14-1822:8; Oshiro 1900:24-1901:7.) Otsuka's internal data therefore establish that aripiprazole was only six times more potent than the 2,3-dichloro propoxy—a result that would have been fully expected. In fact, Dr. Oshiro testified at trial that a six-fold difference in potency between a propoxy compound and a butoxy compound would not have been unexpected. (Oshiro 1772:12-1773:3; 1843:21-1844:6.) In particular, Dr. Oshiro explained that the six-fold improvement in anti-apomorphine stereotypy activity shown from switching the propoxy linker of OPC-4392 to a butoxy linker was neither considerable nor surprising. (Oshiro 1772:12-1773:3; 1843:21-1845:9; PTX 35-T; PTX 37-T.) On direct examination Dr. Oshiro testified that improvement in anti-apomorphine stereotypy potency that he observed when changing the propoxy linker of OPC-4392 to a butoxy linker was neither considerable nor surprising. (Oshiro 1772:12-1773:3) On cross, Dr. Oshiro noted that that difference was six fold. (Oshiro 1843:21-1845:9; PTX 37-T.)

Dr. Oshiro actively participated in the preparation of the Hirose Declaration. When the Hirose Declaration was being drafted, Dr. Oshiro, who at the time was working in Otsuka's intellectual property department, edited the declaration and provided his edits directly to Dr. Hirose. (Oshiro 1793:20-23; Oshiro 1896:9-1897:6.) In addition, Dr. Oshiro attended the same meetings with Dr. Hirose in which the purpose of the Hirose Declaration was explained to be a demonstration of the superiority of the claimed compounds over the prior art. (Hirose 1976:11-1981:19; Hirose 1914:9-21; Oshiro 1874:1-11.) Dr. Oshiro was also undoubtedly aware of

Otsuka's inconsistent internal data as he presented the data to Otsuka in a year-end presentation in 1987. (DTX 59-T; Oshiro 1901:2-20.)

Dr. Oshiro was also well aware of his duty of candor. As an inventor of both of the '416 patent and the '528 patent, Dr. Oshiro has signed two declarations in which he acknowledged his duty of candor pursuant to 37 C.F.R. § 1.56. (DTX 333-A; DTX 116 at OPC0000049 ("I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, § 1.56 .").) Dr. Oshiro testified that when he reads declarations, he makes sure to understand his duties, even if it requires the help of others. (Oshiro 1894:4-1895:15.) Thus, Dr. Oshiro knew he had a duty to disclose material information.

3. ***Otsuka's Statements That There Was No Data Showing That the "Five Exemplary Compounds" Had Antischizophrenic Activity Were False.***

During the reexamination, Otsuka represented to the PTO multiple times that there was no evidence that the five exemplary carbostyril derivatives of the '416 patent, which the examiner based in part her rejections of the '528 patent claims, had antischizophrenic activity. (DTX 121 at 01274, 01348; DTX 459 at OPC0001554; Goolkasian 500:10-501:3.) Yet, Otsuka had prior art data indicating that at least two of these compounds had antischizophrenic activity.

The five exemplary carbostyril derivatives of the '416 patent that the examiner identified are Examples 29, 36, 43, 50, and 54 in the '416 patent. (DTX 121 at 01272-73.) Of these compounds, Otsuka knew that at least Examples 43 and 54 had prior art antischizophrenic activity.

Example 43 is the 5-linked 2-ethoxy propoxy and test compound no. 44 in the Nakagawa declaration. (Oshiro 1881:16-18; Nichols 1655:19-1656:4; DTX 214 at 14.) Example 43 has an ED_{50} value of 0.53 in the Mouse Jumping Test. (DTX 214 at 14.) Dr. Nichols testified that

Example 43 was the most potent compound in the Mouse Jumping Test in the Nakagawa Declaration. (Nichols 1655:19-1656:4; DTX 214 at 14.)

Example 54 is the unsubstituted butoxy and test compound no. 41 in the Nakagawa declaration. (Press 133:5-7; Oshiro 1865:10-1866:3; Oshiro 1881:11-14; DTX 214 at 14.) Example 54 has an ED_{50} value of 5.5 in the Mouse Jumping Test. (DTX 214 at 14.)

Dr. Oshiro had been aware of Otsuka's Mouse Jumping Test data for Example 54. (Oshiro 1867:2-6.)

Otsuka, therefore, knew that its representations to the PTO regarding the five exemplary carbostyril derivatives not having antischizophrenic activity were false and misleading. Dr. Oshiro, in particular, was aware of least Example 54 having antischizophrenic activity.

4. *The Hirose Declaration Was False and Misleading.*

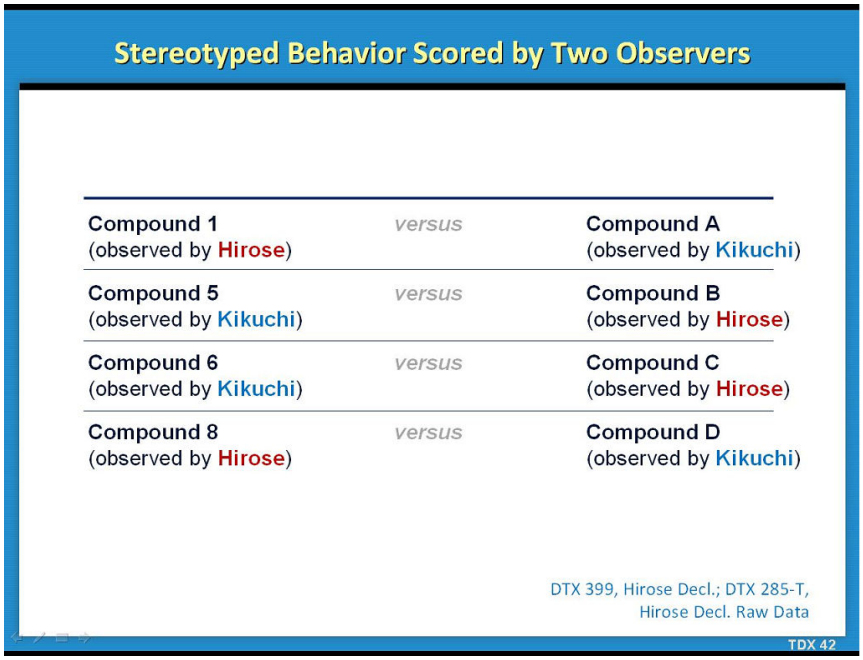
The '528 patent was the sole remaining patent covering aripiprazole at the time Otsuka filed the Hirose declaration. The Hirose declaration (DTX 399) was submitted to overcome the examiner's final rejection during reexamination. If the rejection was not overcome, Otsuka would potentially lose the '528 patent and its monopoly over the ariprazole market—with generic competition arriving much earlier. Otsuka employees, including Drs. Hirose and Oshiro, had more than ten meetings regarding the reexamination and the Hirose declaration. (DTX 4; Hirose 1914:9-21; 1916:11-23; 1970:13-17; Oshiro 1874:1-11.) Those meetings always included the "core group," of Drs. Oshiro, Kikuchi, Yamamoto and Minimikawa, and occasionally included a statistician and members of the Finnegan firm. (Hirose 1916:11-23.) This "core group" comprised Otsuka employees with expertise in pharmacology, organic chemistry, intellectual property, and statistics." (Hirose 1914:9-1918:3.) The first of these meetings occurred two or three years before Dr. Hirose prepared his declaration. (Hirose 1916:11-17.) By the time the meetings were concluded Dr. Hirose knew that his task was to

show that the compounds claimed in the '528 patent were superior to the prior art compounds. (Hirose 1976:11-1980:13; 1986:8-14; Thisted 1471:2-4.) In fact, he believed he was asked specifically to generate data to demonstrate the superiority of the claimed compounds. (Hirose 1976:11-17.)

As discussed in Section III(H)(1), the data submitted in the Hirose declaration were affected by flaws in the experimental methodology. These flaws were hidden from the Examiner by false statements made in the Hirose declaration.

Study Protocol 023155 attached as Exhibit 1 to the Hirose declaration reads that "[t]he observation for stereotyped behavior will be performed by *an observer blind to the treatment received by the mice*." (DTX 399, Ex. 1 at 9 (emphasis added).) A reasonable examiner would have understood the protocol to mean that only one observer scored the stereotyped behavior for all the claimed and prior art compounds and that that observer did not know what compound was being used to treat the mice under observation. (Beninger 957:18-958:8; 958:9-13.)

The raw data and testimony at trial demonstrated, however that two observers—Drs. Hirose and Kikuchi—rather than "an observer," scored stereotyped behavior and that for each claimed compound and its comparative prior art compound, one person observed and scored the anti-stereotypy effect of the claimed compound and another person observed and scored the anti-stereotypy effect of the prior art compound, as shown in the chart below.



(TDX 42 (citing DTX 399, DTX 285-T.) Thus, Dr. Hirose scored the anti-stereotypy effect of aripiprazole, whereas Dr. Kikuchi scored the anti-stereotypy effect of the 2,3-dichloro propoxy compound. (Beninger 937:11-14; Hirose 1986:8-14.)

The evidence also shows that the observers were not blind to the compound being tested and that they both knew the purpose of the experiment. (Beninger 947:5-10; Thisted 1471:2-4; Hirose 1930:20-1931; 1986:8-14; Roth 1302:14-21.)

In short, the protocol that Otsuka represented to the Examiner was followed in its comparative testing, was in fact not followed. (Beninger 947:5-17; 954:22-955:2-10; Miwa Dep. 181:18-182:1 ("In the case of an animal observation test, for example, if the individual who will be observing the behaviors knew what type of compound it had been administered or injected, that information might affect or have some affect, effect on how he or she observes animal or behavior.").)

A reasonable examiner would have considered it important to know how Dr. Hirose actually performed the stereotypy test in order to be able to assess the reliability of the results.

As discussed in Section III(H)(1), the actual methodology of Dr. Hirose's experiment was flawed because due to the subjectivity of the scoring scale, it introduced both confound and bias into the experiment, rendering the data uninterpretable. (Beninger 929:11-21; 956:7-11.)

The bias and confound problem is further highlighted by the fact that Otsuka's own contemporaneous 1987 stereotypy data, which also was not disclosed to the PTO, differs significantly from the test results reported to the PTO. As explained above, in 1987, Otsuka had data showing a mere six-fold difference between aripiprazole and the propoxy dichloro homolog. (DTX 59-T at OPC0717014; Oshiro 1821:16-25.) In the 2005 test data done specifically to show that the butoxy version was better, Otsuka reported a 23-fold difference. (*E.g.*, Roth 1095:25-1096:3.)

From the protocol that Otsuka submitted to the PTO, the examiner would not have been aware that two observers were involved. Nor would the examiner have known that one observer rated aripiprazole and a different observer rated the propoxy dichloro compound to which it was being compared and represented to be superior in the declaration. Nor would the examiner have known that the observers were aware of the identity of the compound that was used to treat the mice they were observing. Nor would the examiner have known that the observers knew that the purpose of the test was to hsow that the butoxy compounds like aripiprazole were superior to their propoxy homologs, not to just evaluate scientific data and reach fair conclusions based on that data. (Beninger 932:1-7; 958:17-959:2; Thisted 1503:16-24.)

Because the Hirose Declaration did not indicate that two observers scored the mice, the PTO did not have sufficient information to be alerted to the confound. When all is said and done, the fact is that Dr. Hirose did not tell the examiner the truth on the protocol. The PTO was

thus deprived of the ability to fairly evaluate the validity of Otsuka's comparative test data on which Otsuka relied to convince the examiner of the patentability of aripiprazole.

IV. CONCLUSIONS OF LAW.

This is a patent infringement case under 35 U.S.C. § 271(e)(2)(A). Defendants are two pharmaceutical companies that filed ANDAs seeking approval to sell generic aripiprazole products for use in the treatment of schizophrenia. Plaintiff Otsuka listed two patents in the FDA Orange Book as covering aripiprazole. The earlier '416 patent entitled "Pharmaceutically Useful Carbostyril Derivatives" (DTX 6) has expired. The later '528 patent-in-suit entitled "Carbostyril Derivatives" (DTX 498) is still in force. Infringement is not at issue. Instead, Defendants challenge the validity and enforceability of the '528 patent on three grounds: (1) nonstatutory, obviousness-type double patenting; (2) obviousness under 35 U.S.C. § 103; and (3) inequitable conduct. Defendants also make the contingent argument that the '528 patent would be invalid under 35 U.S.C. §§ 101 and 112 if the Court were to reject their obviousness defense.

A. BURDEN OF PROOF.

Under ruling case law from the Federal Circuit, Defendants have the burden of proving invalidity by clear and convincing evidence.[11] *American Hoist & Derrick v. Sowa*, 725 F.2d 1350, 1360 (Fed. Cir. 1984). Although this burden applies even when the Defendants rely on evidence that was not before the PTO, "the tribunal considering [the evidence] is not faced with having to *disagree* with the PTO or with *deferring* to [the PTO's] judgment or with taking [the

[11] Apotex (but not Teva) challenges the Federal Circuit rule and contends that the preponderance of the evidence standard ought to be applied throughout the invalidity analysis, or at least when facts not known to the PTO are being considered. Apotex points out that the patent statute does not state any particular level of proof. Apotex contends that in such circumstances, the standard ought to be the normal preponderance of the evidence standard, citing *Massey Junior College, Inc. v. Fashion Institute of Technology*, 492 F.2d 1399, 1403 (C.C.P.A. 1974). Although (continued…)

PTO's] expertise into account." *Id.* at 1359-60 (emphasis in original). In such circumstances, "the patent challenger's burden may be more easily carried." *Connell v. Sears & Roebuck*, 722 F.2d 1542, 1549 (Fed. Cir. 1983).

Furthermore, the ultimate *legal* conclusion of invalidity is not affected by the clear and convincing standard because "[q]uantums of proof relate to proof of facts, not legal conclusions." *Newell Cos. v. Kenney Mfg. Co.*, 864 F.2d 757, 767 (Fed. Cir. 1988); *accord SSIH Equip., S.A. v. ITC*, 718 F.2d 365, 375 (Fed. Cir. 1983) ("[W]e find it inappropriate to speak in terms of a particular standard of proof being necessary to reach a legal conclusion. Standard of proof relates to specific factual questions.").

B. DETERMINATION OF THE PRIOR ART STATUS OF THE NAKAGAWA DECLARATION AND THE WISE POSTER.

During trial the Court provisionally admitted evidence regarding the Nakagawa Declaration (DTX 214) and the Wise Poster (DTX 398), leaving for post-trial briefing and argument whether they are prior art. The Court now holds that both are prior art because both are "printed publications" under 35 U.S.C. § 102(b).[12] Both exhibits are now admitted without restriction.

Apotex's position might be attractive if the Court were starting from scratch, the Court is bound by Federal Circuit precedent and applies the clear and convincing standard.

[12] A "printed publication" becomes prior art against a patentee under § 102(b) if its publication date is more than one year prior to the patentee's U.S. filing date. It is the actual U.S. filing date that controls, so priority obtained under § 119(a) to the earlier Japanese filing date is irrelevant with this kind of prior art. 35 U.S.C. § 119(a), last clause ("but no patent shall be granted on any application for patent for an invention which had been patented or described in a *printed publication in any country more than one year before the date of the actual filing of the application in this country*, or which had been in public use or on sale in this country more than one year prior to such filing") (emphasis added). As explained below, the dates of public availability for both the Nakagawa Declaration and the Wise Poster are more than one year before the October 20, 1989 actual U.S. filing date for the application for the '528 patent.

(continued…)

1. *The Nakagawa Declaration Is Prior Art*

The Nakagawa Declaration is found in the prosecution history of the prior art '416 patent. On March 29, 1988, the date when the '416 patent issued, that prosecution history became accessible to the public. *Bamberger v. Cheruvu*, 55 U.S.P.Q.2d 1523, 1537 n.22 (B.P.A.I. 1998) ("[A] patent file is available to the public on the date a patent issues. 37 C.F.R. § 1.11 (1988)."). Otsuka nevertheless argues that the Nakagawa Declaration is not prior art because the public's only access to it is that prosecution history. Both the Federal Circuit and the PTO, however, have recognized that portions of a prosecution history of a prior art patent are prior art.

In *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350 (Fed. Cir. 2007), the accused infringer relied on test results contained in the prosecution history of the '200 prior art patent. *Id.* at 1357 (The '200 prior art patent "did not disclose experimental data or test results" but its prosecution history "disclosed test results for nine specific compounds."). It also relied on a statement made in a preliminary amendment in the prosecution history of the '779 prior art patent. *Id.* at 1358 ("[A] preliminary amendment in the prosecution history of the ['779] patent contained a statement that" certain compounds are important.). The Federal Circuit did *not* dismiss these prosecution histories from consideration on the ground that they were not prior art. Instead, the Federal Circuit carefully included them as part of the discussion of the relevant prior art. *Id.* at 1357-58. Indeed, when the accused infringer asserted that the district court erred by "exclud[ing] the prosecution history of the '779 patent from the scope of the prior art," the Federal Circuit held that there was no error because the district court had in fact carefully considered that prosecution history. *Id.* at 1363. The accused infringer had raised this last issue

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Accordingly, timing is not the issue. The issue is whether these exhibits are "printed publications."

because the district court had stated that the prosecution history "was not accessible to the public." *Id.* The Federal Circuit held that this statement by the district court was incorrect, but regarded it as harmless error because the prosecution history had in fact been considered in the district court's analysis. *Id.* ("[W]hile the district court may have incorrectly implied that prosecution histories are not accessible to the public, [citations omitted], the court nonetheless considered the prosecution history. . . . [A]ny error committed by the court in this regard was harmless error.").

At every step in its analysis the Federal Circuit in *Takeda* treated the prosecution histories as prior art. It did so when discussing the prior art. 492 F.3d at 1357-58. It did so again when the district court was accused of excluding one of the prosecution histories from the scope of the prior art. *Id.* at 1363. Everything in *Takeda* points towards prosecution histories being part of the prior art, and nothing in *Takeda* suggests the contrary.

In *Bruckelmyer v. Ground Heaters, Inc.*, 445 F.3d 1374 (Fed. Cir. 2006), the Federal Circuit held that drawings from the original application of a Canadian prior art patent that were contained in the prosecution history of the Canadian patent, but not in the issued patent itself, were "printed publications" under § 102(b). The accused infringer needed to rely on these drawings to show that the prior art revealed the method for thawing frozen ground claimed in the patents-in-suit. *Id.* at 1375-76. The Canadian prior art patent did mention thawing frozen ground, but not the details of how to do that. *Id.* at 1376. Those details were in the drawings that had been deleted during prosecution but were still on record in the Canadian prosecution history. *Id.* There was no dispute that the public could request access to the Canadian prosecution history. The "only question" on appeal was "whether a person of ordinary skill in the art interested in the subject matter of the patents-in-suit and exercising reasonable diligence

would be able to locate" the Canadian application. *Id.* at 1378. The Federal Circuit held that the issued Canadian patent's reference to thawing frozen ground was sufficient to guide the skilled person to the application in the prosecution history, and so the drawings were held to be citable prior art. *Id.* at 1379.

In this case, the '416 prior art patent specifically states that its compounds are "useful for central nervous controlling agents such as . . . antischizophrenia agents." (DTX 6 at 3:14-17.) Like the reference to thawing frozen ground in the Canadian patent in *Bruckelmyer*, this statement in the '416 patent is sufficient to guide the skilled person to the Nakagawa Declaration in the prosecution history of the '416 patent.

In *Bamberger v. Cheruvu*, 55 U.S.P.Q. 2d 1523, 1536-37 (B.P.A.I. 1998), one of the parties to a PTO interference proceeding relied on test results in a declaration in the prosecution history of a prior art patent as prior art. The PTO's Board of Appeals and Interferences treated that declaration as prior art. *Id.* at 1537 n.22 ("We have assumed that the Welborn declaration in the file of the Welborn patent is prior art under 35 U.S.C. Section 102(b), given that the patent issued more than one year prior to the date Cheruvu filed the application which matured into the Cheruvu patent and a patent file is available to the public on the date a patent issues. 37 C.F.R. Section 1.11 (1988) ").

Otsuka has cited no case holding that the contents of the prosecution history of a prior art patent are not prior art. In view of *Takeda*, *Bruckelmyer*, and *Bamberger*, the Court holds that the Nakagawa Declaration (DTX 214) is prior art.[13]

[13] Defendants also assert that the Nakagawa Declaration is prior art under 35 U.S.C. § 102(a). (*See* D.I. 324 at 8-9.)

2. *The Wise Poster Is Prior Art.*

Dr. Lawrence Wise was a group leader of the antipsychotic drug discovery project at Warner-Lambert and is one of the authors listed on the Wise Poster. (DTX 398.) At his deposition he explained the circumstances under which the Wise Poster was publicly disclosed and distributed at the 1987 Society for Neurosciences Conference. (Wise Dep. 39:4-17.) Dr. Wise's poster session was a half-day standard poster session related to potential drugs. (*Id.* at 15:17-16:7.) When questioned in his deposition if he could describe what his poster looked like Dr. Wise responded, "[Y]es. I know exactly what [my poster] looked like. It looks exactly like the hand-outs that [Plaintiffs] have today." (*Id.* at 22:20-22.) When questioned if he kept personal files of this 1987 poster presentation, he testified that he "has a file at home that has posters and presentations and patents [he] gave or generated during [his] employment," and that he kept this file in chronological order. (*Id.* at 49:7-19.) Dr. Wise recalled that he made his poster with a "photographic process" so that he could not only have a large poster to display but also smaller duplicate copies to use as hand-outs. (*Id.* at 23:1-9.) Dr. Wise testified that he took between "a hundred and two hundred copies" of his poster presentation in handout form to distribute at the presentation, and he specifically recalled handing out in excess of a hundred of those poster handouts at the 1987 Conference. (*Id.* at 33:20-34:6.) The Court also notes that DTX 398 appears on its face to be exactly what Dr. Wise testified it to be. In particular, the upper left hand corner of DTX 398 states "Soc. Neurosciences" and has the date "1987." In addition, DTX 398 looks like what one would expect of a poster to be displayed at a conference. Accordingly, the Court holds that the evidence authenticates the Wise Poster (DTX 398) under Fed. R. Evid. 901(b)(1) (testimony of a witness with knowledge) and (4) (the appearance, contents, and substance of the document itself).

Under the controlling Federal Circuit precedent of *In re Klopfenstein*, 380 F.3d 1345 (Fed. Cir. 2004), and *Massachusetts Institute of Technology. v. AB Fortia*, 774 F.2d 1104 (Fed. Cir. 1985), the Wise Poster qualifies as a prior art printed publication under § 102(b), having been made publicly available more than one year before Otsuka's October 20, 1989 U.S. filing date for the '528 patent. Otsuka has come forward with no contrary evidence or basis on which to dispute Dr. Wise's testimony that the Wise Poster is authentic and was publicly disclosed and distributed.

Otsuka challenges the Wise Poster's admissibility on the grounds of lack of "corroboration," citing *Finnigan Corp. v. International Trade Commission,* 180 F.3d 1354 (Fed. Cir. 1999). Neither *Finnigan* nor any other case cited to the Court holds that there is a legal requirement to corroborate a document asserted to be a *printed publication*. Rather, *Finnigan* is about the inadequacy of uncorroborated oral testimony to prove a prior "public use," which is a different kind of prior art also referenced in § 102(b). Nowhere does *Finnigan* ever mention requiring corroboration of a "printed publication" as opposed to a "public use." A printed publication, being in the form of a writing, speaks for itself and does not require oral testimony or other evidence to express its technical contents. A public use is an entirely different animal. It requires evidence to establish its technical content. If such evidence is only *oral* evidence, it needs help. After all, the finder of fact needs assurance that the witness correctly remembers the exact technical details, such as whether Tab A went into Slot B rather than Slot C. With a printed publication, there is no comparable problem. The document says what it says.

The Federal Circuit's decisions in *Klopfenstein* and *MIT* are controlling here, not *Finnigan*. Notably, neither *Klopfenstein* nor *MIT* articulate a corroboration requirement for printed publications.

In *Klopfenstein*, the Federal Circuit upheld the denial of a patent application based on a slide presentation held to be a printed publication under § 102(b). The printed slide presentation was displayed at an American Association of Cereal Chemists. 380 F.3d at 1347. This slide presentation was printed and pasted onto poster boards. *Id.* No copies of the presentation were disseminated and the presentation was never catalogued or indexed in any library or database. *Id.* Appellants argued that the slide presentation was not a "printed publication" for purposes of § 102(b) because there was a lack of evidence that the presentation was copied, distributed, or catalogued in any database or library. *Id.* at 1348. The Federal Circuit determined that the slide presentation was indeed § 102(b) prior art—even though it was never reduced to a paper copy and distributed. *Id.* at 1352.

In *MIT*, a paper was presented orally "by Dr. Levine of the MIT group to the First International Cell Culture Congress in Birmingham, Alabama, September 21-25, 1975. The conference was attended by 50 to 500 cell culturists. Prior to the conference Dr. Levine gave a copy of the paper to the head of the conference. Afterward, copies were distributed on request, without any restrictions, to as many as six persons, more than one year before the filing date of the '534 and '654 patents." 774 F.2d at 1108-09. This paper was held to be a § 102(b) printed publication. *Id.* at 1109.

The facts here concerning public availability and dissemination of the printed publication are even more compelling than those of *Klopfenstein*, and similar to the facts of *MIT*. The Wise Poster was both publicly displayed and distributed as a handout at the Society for Neurosciences Conference in November of 1987. (Wise Dep. 15:17-16:17; 33:20-34:6; 39:4-17.) Dr. Wise has specific recollection of attending that meeting because it was his first trip to New Orleans. (*Id.* at 12:20-13:4.) Dr. Wise's testimony (*id.* at 30:17-31:3; 32:10-32:17; 33:13-15; 33:20-34:6) that he

handed out over a hundred posters at the conference easily establishes that it is a printed publication under § 102(b). *MIT*, 774 F.2d at 1109 ("As the Commission noted, between 50 and 500 persons interested and of ordinary skill in the subject matter were actually told of the existence of the paper and informed of its contents by the oral presentation, and the document itself was actually disseminated without restriction to at least six persons.").

Nevertheless, even if corroboration were required, and it is not, one of Otsuka's own documents provides corroboration that the Wise Poster was presented at the 1987 Society for Neuroscience Conference in Louisiana. The September 5, 1988 memorandum from Shinichiro Haruki to Manager Kabe (the "Haruki Memo," DTX 274-T) specifically discusses details that are consistent with Dr. Wise's testimony. The Haruki Memo tells us that Parke-Davis reported on the coumarin compound PD 116795 at the 1987 Society for Neuroscience Conference in Louisiana. (DTX 274-T at OPC0730595.) The compound PD 116795 is shown in the Wise Poster, and the poster was shown at the 1987 Society for Neuroscience Conference in Louisiana. (DTX 398.) The Haruki Memo reports that this coumarin compound has presynaptic agonist properties, just as the Wise Poster reports. (DTX 274-T at OPC0730595; DTX 398; Castagnoli 814:24-815:13.) These statements in the Haruki Memo are consistent with the Wise Poster being shown in 1987 at the Society of Neuroscience Conference in Louisiana and therefore corroborate the document and Dr. Wise's testimony.

In summary, the Wise Poster is established as § 102(b) prior art and is admitted into evidence without restriction.

C. THE ASSERTED CLAIMS ARE INVALID FOR NONSTATUTORY, OBVIOUSNESS-TYPE DOUBLE PATENTING.

Defendants assert invalidity for obviousness-type double patenting in view of claim 13 of Otsuka's prior '416 patent. "The doctrine of double patenting is intended to prevent a patentee

from obtaining a timewise extension of [a] patent for the same invention or an obvious modification thereof." *Sun Pharm. Indus. v. Eli Lilly & Co.*, 611 F.3d 1381, 1384 (Fed. Cir. 2010) (quoting *In re Basell Poliolefine Italia S.P.A.*, 547 F.3d 1371, 1375 (Fed. Cir. 2008)). "Same invention" double patenting, also known as statutory double patenting, is premised on 35 U.S.C. § 101 , and prohibits an inventor from obtaining a later patent covering the same invention as an earlier patent. By contrast, obviousness-type double patenting does not require that the *same* invention be claimed in the later claim; rather, it is a judicially created doctrine that prohibits an inventor from obtaining a patent covering "an *obvious variation* of an invention disclosed and claimed in an earlier patent by the same inventor." *Georgia-Pacific Corp. v. U. S. Gypsum Co.*, 195 F.3d 1322, 1326 (Fed. Cir. 1999) (emphasis added).

The doctrine of obviousness-type double patenting is grounded in public policy. *Georgia-Pacific*, 195 F.3d at 1326; *In re Longi*, 759 F.2d 887, 892 (Fed. Cir. 1985). As the Federal Circuit has explained, "[t]he public should . . . be able to act on the assumption that upon the *expiration* of the patent it will be free to use not only the invention claimed in the patent but also modifications or variants which would have been *obvious* to those of ordinary skill in the art." *Id.* at 892-93 (quoting *In re Zickendraht*, 319 F.2d 225, 232 (C.C.P.A. 1963) (Rich, J. concurring)) (emphasis in original).

Obviousness-type double patenting can apply where the earlier patent and later patent are not part of the same patent family and issue from separate parent applications. *Sun Pharm.*, 611 F.3d at 1389 (holding the '826 patent-in-suit invalid for obviousness-type double patenting in view of the earlier '614 patent that issued from a different patent family); *In re Berg*, 140 F.3d 1428, 1435 n.7 (Fed. Cir. 1998) (rejecting claims for obviousness-type double patenting over claims in a patent that were "not related as by continuation, continuation-in-part, or divisional").

Obviousness-type double patenting does not require that the earlier and later patents derive from a common patent application. *Sun Pharm.*, 611 F.3d at 1383; *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 999 (Fed. Cir. 2009); *Berg*, 140 F.3d at 1435 n.7; *Longi*, 759 F.2d at 889. Nor do the earlier and later patents need to have the same inventive entities, as long as the patents share a common assignee. *In re Fallaux*, 564 F.3d 1313, 1315 (Fed. Cir. 2009); *Longi*, 759 F.2d at 893.

Further, a reference patent whose claim is used for an obviousness-type double patenting rejection may be either a non-prior art or a prior art patent. Indeed, the Federal Circuit routinely considers prior art patents as a basis for such rejections. *Procter & Gamble*, 566 F.3d at 998-99 (addressing obviousness-type double patenting using a reference claim in a § 102(e) prior art patent); *Longi*, 759 F.2d at 896 (affirming a holding of obviousness-type double patenting because the claims at issue were obvious over claims in four prior art patents); *see also Geneva Pharm., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1385 (Fed. Cir. 2003) (noting that in a double patenting analysis, an earlier patent's disclosure is not generally considered unless "that patent qualifies as prior art under 35 U.S.C. § 102"). The principle that a prior art patent can be a basis for double patenting has a long history. *In re Ward*, 236 F.2d 428, 432 (C.C.P.A. 1956) (affirming double patenting rejection because the claims were obvious modifications of applicant's earlier § 102(e) prior art patent).

1. *Obviousness-Type Double Patenting Standard.*

An obviousness-type double patenting analysis involves two steps: "First, as a matter of law the court construes the claim in the earlier patent and the claim in the later patent and construes the differences. Second, the court determines whether the differences in subject matter between the two claims render the claims patentably distinct." *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 968 (Fed. Cir. 2001) (citing *Georgia-Pacific*, 195 F.3d at 1326-27). Two

claims are not "patentably distinct" if the later claim would have been obvious to a person of ordinary skill in the art based on the earlier claim, in light of additional prior art. *Longi*, 759 F.2d at 893. "An absence of overlap between the later claim and the earlier claim does not preclude a conclusion that the later claim is patentably indistinct from the earlier claim." *Eli Lilly v. Barr*, 251 F.3d at 968 n.6; *accord In re Lonardo*, 119 F.3d 960, 967 (Fed. Cir. 1997); *Longi,* 759 F.2d at 896 n.9; *Zickendraht*, 319 F.2d at 232.

2. *Differences Between Obviousness-Type Double Patenting and Statutory Obviousness.*

Obviousness-type double patenting and obviousness are two distinct defenses with separate legal requirements. These two defenses differ in several significant ways.

An obviousness-type double patenting analysis must begin with the claim of an earlier-issued patent. *Eli Lilly v. Barr*, 251 F.3d at 968; *Procter & Gamble*, 566 F.3d at 999; *Geneva*, 349 F.3d at 1378 n.1. Thus, unlike in an obviousness analysis, there is no requirement that the person of ordinary skill in the art be motivated to select the invention claimed in the earlier patent as a starting point. In other words, because the starting point for a double-patenting analysis, is, by definition, the claims of an earlier patent, there is no requirement to identify a "lead compound." One might even say that the patentee already selected its "lead compounds" by choosing to claim them in the earlier patent.

Unlike in an obviousness analysis, "double patenting does not require inquiry into a motivation to modify the prior art." *Procter & Gamble*, 566 F.3d at 999; *Geneva*, 349 F.3d at 1378 n.1; *Astellas Pharma, Inc. v. Ranbaxy, Inc.*, No. 05-2563 (MLC), 2007 WL 576341, at *4 (D.N.J. Feb. 21, 2007) (Cooper, J.).

Double patenting, unlike obviousness, "does not require inquiry into objective criteria suggesting non-obviousness." *Id.*

Finally, while § 103 obviousness completely precludes patentability, an obviousness-type double patenting rejection in the PTO can be overcome with a terminal disclaimer so that the later patent expires when the earlier one does. *Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1375, 1388 (Fed. Cir. 2005); *Longi*, 759 F.2d at 894. Otsuka filed no such terminal disclaimer.

3. *The Asserted Claims Are Not Patentably Distinct from Claim 13 of the '416 Patent.*

Claim 13 of Otsuka's earlier '416 patent claims the unsubstituted butoxy compound. The structures of aripiprazole and the unsubstituted butoxy are identical except for the substituents at the 2 and 3 positions of the phenyl ring. (Press 100:18-23.) Aripiprazole has chlorine atoms at those positions, whereas the unsubstituted butoxy has hydrogen atoms. (Press 101:14-21.)

The prior art teaches the unsubstituted butoxy compound's usefulness as an antischizophrenic agent. For example, the '416 patent itself states that its claimed compounds "are useful for central nervous controlling agents such as . . . antischizophrenia agents." (DTX 6 at 3:13-16.)[14] The Nakagawa Declaration reports that the unsubstituted butoxy has "excellent" activity in the mouse jumping test that, per Otsuka's own representations during the prosecution of Otsuka's earlier '932 patent, is a test method for determining antischizophrenic activity. (DTX 214 at 14; DTX 471 at 4.)

Otsuka now argues that the '416 patent describes the unsubstituted butoxy solely as an antihistamine, but it previously presented sworn testimony to the PTO that a person of ordinary skill would understand from the '416 patent that *all* of the claimed compounds (including the

[14] Normally, the "earlier patent's disclosure [*i.e.*, the written description other than the claims] is not available to show nonstatutory double patenting." *Geneva*, 349 F.3d at 1385. There are exceptions to this principle. For example, "the earlier patent's disclosure may register on the patentability scale if that patent qualifies as prior art under 35 U.S.C. § 102, which is generally not the case." *Id.* Such *is* the case here, however, as there is no dispute that the '416 patent is (continued…)

unsubstituted butoxy) have *both* antihistaminic and central nervous system controlling activity. (Bodor Dep. 12:11-13:3.) Furthermore, claims of the '416 patent indicate that carbostyril derivatives can have both "an antihistaminic and a central nervous controlling effect." (DTX 6 at claims 40, 77, 80, 88, and 92.) In addition, the '416 patent actually claims the unsubstituted butoxy as a "central nervous controlling agent" because claim 21 recites "[a] central nervous controlling agent, containing a suitable amount of a carbostyril derivative . . . according to claim 1," and claim 1 covers the unsubstituted butoxy compound. (DTX 6 at 69:26-70:12, 71:8-11; Press 120:22-121:5.) Most tellingly, Otsuka's own expert Dr. Roth testified at trial that at least some antischizophrenic drugs are also antihistaminics (Roth 1385:5-1387:21), and so even if the unsubstituted butoxy were in fact an antihistaminic (something that was not proved at trial), it could still also be an antischizophrenic. Accordingly, the prior art's teaching that the unsubstituted butoxy compound would be useful as an antischizophrenic agent is not refuted by Otsuka's antihistamine argument.

Accordingly, the only difference between (a) the unsubstituted butoxy compound of claim 13 of the prior '416 patent and (b) claims 12, 17, and 23 of the '528 patent is the chlorine atoms at positions 2 and 3 of the phenyl ring of the aripiprazole molecule. The evidence at trial established that, in this case, the substitution of chlorine at the 2 and 3 positions of the phenyl ring of the unsubstituted butoxy would have been a logical, routine, and obvious modification to the person of ordinary skill based on the Nakagawa Declaration and Otsuka's foreign counterparts to the '416 patent. (Press 140:15-141:10.)

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prior art. Accordingly, all the teachings in the '416 patent are to be considered in the double patenting analysis.

As Dr. Press and Dr. Castagnoli testified, the mouse jumping data from Table 8 of the Nakagawa Declaration would point the person of ordinary skill directly to the addition of chlorine at the 2 and 3 positions on the phenyl ring. (Press 132:1-137:12; Castagnoli 736:12-737:24.) The Nakagawa Declaration provides data showing that a propoxy compound with chlorine at the 2 position of the phenyl ring and a propoxy compound at the 3 position of the phenyl ring were each more potent antischizophrenic agents than the unsubstituted propoxy compound. (Press 135:20-137:3; Castagnoli 736:12-737:24.) Because propoxy and butoxy compounds are homologs, the person of ordinary skill would presume that they behave similarly, and that a butoxy compound with chlorines at the 2 and/or 3 positions would likewise be more potent than the unsubstituted butoxy compound. (Press 137:6-138:4.)

Although the Nakagawa Declaration does not have data on a 2,3-dichloro substituted compound, it would have been obvious for the person of ordinary skill to put chlorine atoms at both the 2 and 3 positions of the phenyl ring. Otsuka's own prior art patent applications DE '105 and SE '945 disclose the 2,3-dichloro propoxy compound, which has chlorines at *both* the 2 and 3 positions of the phenyl ring. (DTX 248-T at 68; Castagnoli 806:19-807:22; DTX 1159-T at 62; Press 138:8-139:16.) SE '945 additionally discloses that its compounds are useful as antischizophrenic agents. (DTX 1159-T at 5; Press 139:18-24.) Otsuka's prior art compound OPC-4392 was likewise a 2,3-di-substituted compound, although the substitution was methyl rather than chlorine. (Press 145:22-146:10; Castagnoli 659:18-661:24.) Parke-Davis's prior art patent on treating schizophrenia with coumarin compounds also disclosed a compound with chlorine at both the 2 and 3 positions on the phenyl ring. (DTX 629 at 2:15, 11:45-46; Castagnoli 656:17-657:1.)

In view of the foregoing, the person of ordinary skill would have considered the substitution of chlorine atoms at the 2 and 3 positions of the phenyl ring of the unsubstituted butoxy to be routine optimization and a logical step in improving antipsychotic potency of the unsubstituted butoxy of claim 13 of the '416 patent. Aripiprazole is, therefore, an obvious variant of the unsubstituted butoxy. Accordingly, Otsuka's claims covering aripiprazole are invalid under the nonstatutory, obviousness-type double patenting doctrine that precludes a second patent on obvious variants of what is claimed in an earlier patent. *Basell Poliolefine*, 547 F.3d at 1375; *Georgia-Pacific*, 195 F.3d at 1326-29; *Longi*, 759 F.2d at 892-97.

The *In re Zickendraht*, 319 F.2d 225 (C.C.P.A. 1963), case is strikingly similar to the case at bar. In *Zickendraht*, there were two differences between the applicants' claimed compound and the compound claimed in the applicant's earlier patent. *Id.* at 228. The second of the two differences was the presence of a substituent such as chlorine on the benzene ring of the molecule in the earlier claim and the absence of any substituent in the later claim. *Id.* None of the differences, either alone or in combination, were sufficient to overcome the PTO's double patenting rejection that was affirmed by the court. The later claims were merely "modifications or variants" of the earlier claims "which would have been obvious to those of ordinary skill in the art at the time the invention was made, taking account the skill of the art and prior art other than the invention claimed in the issued patent." *Id.* at 232 (Rich, J., concurring). Similarly here, the only difference between aripiprazole and the unsubstituted butoxy of claim 13 of the '416 patent is the presence of chlorine substituents. (Press 100:18-23.) The person of ordinary skill in the art, however, would have considered this difference to be only a routine and obvious modification. Aripiprazole is, therefore, an obvious variant of the unsubstituted butoxy.

Accordingly, Otsuka's asserted claim 12 of the '528 patent, which claims the compound aripiprazole, is invalid for double patenting. Otsuka offered no evidence at trial that would distinguish claims 12, 17, and 23 from one another with regard to obviousness-type double patenting. Essentially they will stand or fall together. Claim 17 is directed to a pharmaceutical composition for treating schizophrenia. A person having ordinary skill in the art in possession of the unsubstituted butoxy, having modified it to aripiprazole would have routinely placed the compound into a composition. (Press 141:11-142:5.) Similarly, because claim 23 is directed to a method of treating schizophrenia in a patient using aripiprazole, and the treatment of schizophrenia was the basis for modifying the unsubstituted butoxy, claim 23 is also an obvious variant of claim 13 of the '416 patent. (Press 142:6-19.)

Because a motivation to modify and secondary considerations of nonobviousness do not play a role in the obviousness-type double patenting analysis, the Court's inquiry on that issue can end at this point. Even if a motivation to modify were required, however, that motivation is provided by the Nakagawa Declaration and the other prior art discussed above, which provide strong suggestions to add chlorine at positions 2 and 3 on the phenyl ring with a "high expectation" of improved potency. (Press 168:25-169:2.) Furthermore, even if secondary considerations were taken into account, the conclusion would still be invalidity. As explained below in Section IV(D)(4), the evidence of secondary considerations is weak in this case. Moreover, such evidence cannot overcome a strong showing of obviousness, which is the case here. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1372 (Fed. Cir. 2007); *Newell*, 864 F.2d at 768. Therefore, even if obviousness-type double patenting required an analysis more like statutory obviousness, the conclusion would still be invalidity.

In view of the foregoing, the Court holds that Claims 12, 17, and 23 of the '528 patent are invalid for obviousness-type double patenting.

D. THE ASSERTED CLAIMS ARE INVALID FOR OBVIOUSNESS UNDER § 103.

KSR International Co. v. Teleflex Inc., 550 U.S. 398 (2007), is the most recent Supreme Court case dealing with obviousness. Its analysis is based on the statute.

> Section 103(a) forbids issuance of a patent when "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains."

KSR, 550 U.S. at 406. *KSR* reaffirms that *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966), requires an "objective" analysis. *KSR*, 550 U.S. at 406. Four factors must be examined, namely: (1) "the scope and content of the prior art"; (2) the "differences between the prior art and the claims at issue"; (3) "the level of ordinary skill in the pertinent art"; and (4) any "secondary considerations" that "might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented." *Id.* "While the sequence of these questions might be reordered in any particular case, the factors define the inquiry that controls." *Id.* at 407. The Court's findings regarding each of these factors are set forth above in the Court's Findings of Fact.

Aripiprazole is a member of the prior art genus of carbostyril derivatives disclosed in the prior art '416 patent and its foreign counterparts. Defendants assert that the compound aripiprazole, and its use for treatment of schizophrenia, is unpatentable for obviousness in view of that prior art genus, particularly in light of prior art not considered by the PTO. Defendants have focused on three exemplary compounds from that prior genus, namely, the 2,3-dichloro propoxy homolog of aripiprazole, the unsubstituted butoxy compound discussed above, and OPC-4392 (a 2,3-dimethyl analog of aripiprazole).

According to Otsuka, attention must be focused solely on prior art clozapine and risperidone derivatives, and none given to prior art carbostyril derivatives. Otsuka's attempt to eschew all carbostyril derivatives is belied by the fact that all the proceedings in the PTO centered on prior art carbostyril derivatives. Furthermore, the law would not permit one to ignore carbostyril derivatives even if one assumes *arguendo* that clozapine and risperidone derivatives are suitable starting places. For example, in *In re Lamberti*, 545 F.2d 747, 750 (C.C.P.A. 1976), the court held that, even though *symmetric* dialkyls were preferred in the prior art, prior art *asymmetric* dialkyls must also be considered because "all disclosures of the prior art, including unpreferred embodiments, must be considered." *See also In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004) (Federal Circuit precedent "does not require that a particular combination must be the preferred, or the most desirable, combination described in the prior art in order to provide motivation for the current invention."); *Merck & Co. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989) (The fact that the prior art "discloses a multitude of effective combinations does not render any particular formulation less obvious."); *Carter-Wallace, Inc. v. Otte*, 474 F.2d 529, 543 (2d Cir. 1972) ("[A] development cannot be regarded as unobvious simply because it was not the first, or even the second or third, structural change of which a researcher would think."); *id*. at 545 ("[A]lthough 'it is not possible to say that the state of the art was such as to make carbamate esterfication of the propanediols of Berger I the preeminent suggestion of the art or the evident first choice of the investigator interested in improved and prolonged mephensin-like properties', still 'carbamate esterfication of substituted propanediols was among the suggestions with which the prior art was enriched.'") (quoting *Carter-Wallace, Inc. v. Davis-Edwards Pharmacal Corp.*, 341 F. Supp. 1303, 1311-12 (E.D.N.Y. 1972)).

Accordingly, even if as Otsuka suggests a skilled person might think to pursue development of noncarbostyril compounds, such as clozapine or risperidone derivatives, that does not disqualify carbostyrils from *also* being good compounds for development. The law is clear that the prior art can point to multiple starting points for further development. *E.g.*, *Altana Pharma AG v. Teva Pharm. USA, Inc.*, 566 F.3d 999, 1008 (Fed. Cir. 2009) ("[T]o the extent [plaintiff] suggests that the prior art must point to only a single lead compound for further development efforts, that restrictive view of the lead compound test would present a rigid test similar to the teaching-suggestion-motivation test that the Supreme Court explicitly rejected in *KSR*.").

1. *Obviousness Based on the 2,3-Dichloro Propoxy Compound.*

Aripiprazole, and each of the other butoxy carbostyril derivatives claimed in the '528 patent, is a member of the much larger genus of carbostyril derivatives disclosed in Otsuka's prior art '416 patent. There is usually nothing nonobvious about selecting a small group of compounds from a large group of prior art compounds—unless there is a "special significance" to the small group that differentiates them from the prior art genus.

> The position of the Patent Office is, essentially, that Lemin has done no more that pluck a subgenus out of a generic disclosure by Jones, and has used that subgenus in precisely the manner taught by Jones.
>
> Generally speaking, there is nothing unobvious in choosing 'some' among 'many' indiscriminately. *In re Rosicky*, 47 C.C.P.A. 859, 276 F.2d 656, 125 U.S.P.Q. 391. 859. Here, however, the choice is based on a discovery by Lemin that some compounds, falling within a prior art genus, have a special significance.

In re Lemin, 332 F.2d 839, 841 (C.C.P.A. 1964); *see also In re Susi*, 440 F.2d 442, 445-46 (C.C.P.A. 1971) (Obviousness affirmed because applicant was "in the position of one who argues that the selection of a relatively small subgenus from a genus disclosed in the prior art" is

patentable and the applicant had failed to demonstrate that his "relatively small class of additives is superior, as a class, to the much larger classes disclosed" in the prior art.).

This presents what is sometimes referred to as the problem of a "selection invention." *In re Krazinski*, 347 F.2d 656, 661 (C.C.P.A. 1965). The typical way in which the law analyzes such cases is to compare the newly claimed compound to the closest compound in the prior art genus in order to determine whether the claimed compound has unexpectedly superior properties. *Id.* at 661-62. It is at least impractical, and sometimes impossible, to compare the claimed compound to *every* member of the prior art genus. *Id.* at 662. Instead, the closest prior art compound stands in as representative for the entire prior art genus of compounds. The thought is that, if the claimed compound is unexpectedly superior to its closest neighbor in the genus, then it is probably superior to the other members of the genus because one would expect the nearest neighbor to be the one most likely to share the improved properties.

The law particularly favors using one of "the next adjacent homologs" of the claimed compound as the closest prior art compound for comparison purposes. *Krazinski*, 347 F.2d at 662; *accord In re Wilder*, 563 F.2d 457, 458 n.7, 460 (C.C.P.A. 1977). In this case, a difference of one methylene group in the linker (*i.e.*, one more or one fewer link in the chain) would be a next adjacent homolog of aripiprazole. (Press 98:7-25; Goolkasian 504:21-505:15.) The lower adjacent homolog would therefore be a compound with a propoxy linker with three carbons versus aripiprazole's butoxy linker with four carbons. (Press 98:7-25; Goolkasian 510:18-511:8.) The 2,3-dichloro propoxy compound that is disclosed in the DE '105 and SE '945 patents is that next lower homolog of aripiprazole. (Press 139:18-24; Goolkasian 475:20-22; Castagnoli 806:19-808:10.) Accordingly, one would look to a comparison between aripiprazole and the prior art 2,3-dichloro propoxy compound in order to ascertain whether or not the

selection of aripiprazole from the prior art genus of carbostyril derivatives is deserving of patent protection.

The reexamination of the '528 patent-in-suit culminated with this very comparison being made. *See Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1383 (Fed. Cir. 2005) ("[T]he district court should review the file history as part of its assessment of whether the invention claimed by the claims in suit are nonobvious."). Earlier in the reexamination, the examiner twice rejected the claims based on the DE '105 prior art patent, but did not specifically mention the 2,3-dichloro propoxy compound. (DTX 121 at 01238-43, 01322-28.) After an interview, however, attention was focused upon the prior art 2,3-dichloro propoxy compound. (DTX 121 at 01357 ("As discussed and agreed to during the interview with the Examiner, such comparative compounds [including the 2,3-dichloro propoxy compound] constitute the closest prior art.").) Otsuka submitted Dr. Hirose's Declaration and argued that it demonstrates that aripiprazole has unexpectedly superior potency over the prior art 2,3-dichloro propoxy compound. (DTX 121 at 01355-63.) The examiner's statement of "Reasons for Patentability/Confirmation" shows that she was persuaded by Otsuka's submissions:

> The compounds [of] claims 1-21 are found to be allowable since applicants have compared their compounds with the closest prior art. The ones with just one difference in the linker chain, propyloxy [a/k/a propoxy] to a butoxy chanin [sic, chain] shows a clear unexpected result in the ED50 values.

(DTX 121 at 01412.)

The examiner knew of the close structural similarity between aripiprazole and the 2,3-dichloro propoxy compound. (DTX 121 at 01356-58, 01366-69.) She also knew that the '416 patent covers the genus that includes both those compounds and that it states that its compounds are useful as antischizophrenic agents. (DTX 121 at 01239, 01324, 01357, 01367-68.) That was sufficient to raise the inference that the two compounds have similar properties, so as to require

Otsuka to come forward with evidence of unexpected superiority. *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 2006 WL 2008962 (E.D. Va. 2006), *rev'd*, 499 F.3d 1293, 1301 (Fed. Cir 2007); *In re Payne*, 606 F.2d 303, 313-16 (C.C.P.A. 1979); *In re Swan Wood*, 582 F.2d 638, 641-42 (C.C.P.A. 1978).

This is confirmed by additional prior art not disclosed to the PTO. For example, Otsuka's SE '945 published patent application discloses the 2,3-dichloro propoxy compound in its Example 134 and recites that its compounds are intended as antischizophrenic agents. (DTX 1159-T at 5, 61; Press 139:18-24.) Parke-Davis's '456 patent discloses the 2,3-dichloro propoxy isostere of the 2,3-dichloro propoxy carbostyril and recites that its compounds are intended as antischizophrenic agents. (DTX 629 at Abstract, 2:16, 5:33, 11:45.) In the Nakagawa Declaration, the 2-chloro propoxy and 3-chloro propoxy compounds, which are very close in structure to the 2,3-dichloro propoxy compound, did "excellent" in the mouse jumping test, which is an indicator of antischizophrenic potential. (DTX 214 at 14; DTX 471 at 4 (mouse jumping is a test for antischizophrenic behavior); Press 135:18-137:7; 252:14-18, 255:12-16; Marshall 381:14-389:17; Castagnoli 736:7-737:24.) Such evidence cements the inference that the 2,3-dichloro propoxy compound and compounds structurally similar to it, such as aripiprazole, would have been expected to be useful to treat schizophrenia, so that Otsuka had to come forward with evidence of unexpected superiority. *In re Dillon*, 919 F.2d 688, 692, 696 (Fed. Cir. 1990) (en banc); *In re Merck & Co.*, 800 F.2d 1091, 1097-98 (Fed. Cir. 1986); *Wilder*, 563 F.3d at 460.

Furthermore, structure activity relationship tests reported in the Nakagawa Declaration and the Wise Poster, which were not known to the reexamination examiner, suggest that a change from a propoxy linker to a butoxy linker would result in a compound with increased

antipsychotic activity. This meets even the strictest possible requirement for a teaching/suggestion/motivation ("TSM") to change from a propoxy to a butoxy linker (the Supreme Court rejected an overly strict application of the TSM test in *KSR*, 550 U.S. at 407, 415-422). This also refutes Otsuka's argument that an improvement from making that change would be "unexpected."

The Nakagawa Declaration's data from the Mouse Jumping Test include a head-to-head comparison between an unsubstituted *propoxy* carbostyril compound that had a test score of 9.3 mg/kg and an unsubstituted *butoxy* carbostyril compound that had a test score of 5.5 mg/kg. (DTX 214; DTX 208-T at OPC0616309 (corroborates accuracy of 5.5 ED_{50} value for unsubstituted butoxy in the Nakagawa Declaration); Press 134:15-135:15; 140:22-141:10; Goolkasian 537:8-538:1; Castagnoli 671:11-672:14; Oshiro 1848:7-1849:11; 1852:9-1853:18; 1867:8-1870:1.) Because a lower score in the mouse jumping test means greater potency, this pair of data in the Nakagawa Declaration would have taught a person of ordinary skill that greater antischizophrenic potency can be expected from going from a propoxy linker to a butoxy linker. (Press 140:22-141:10, 163:23-166:11; Castagnoli 671:11-672:14.) Moreover, as Dr. Press explained, "a propoxy to butoxy is a very related compound" and so a medicinal chemist would expect that the effects of chlorine substitution on the propoxy series "would be directly applicable to the butoxy series." (Press 137:15-138:14; 98:7-99:16.)

During trial Otsuka took great pains to try to establish that a better score in the mouse jumping test would not correlate to a better score in the anti-apomorphine stereotypy test which is the test used in the Hirose Declaration. As indicated in Section III(E)(1)(A) of the Court's Findings of Fact Defendants have the better evidence on this issue. (Marshall 2189:23-2194:9 (explaining DTX 375 and DTX 509).) More importantly, the dispute is actually beside the point.

The bottom line take away from the Hirose Declaration, and the attorney arguments that accompanied it, is that switching from a propoxy to a butoxy linker is said to yield unexpectedly better potency in the *treatment of schizophrenia*. Better potency in the anti-apomorphine stereotypy test was merely the means chosen by Otsuka to try to establish that conclusion. Other tests, the Mouse Jumping Test being among them, could also serve to establish or refute that conclusion. (DTX 20, Col. 43:7-8; Marshall 381:14-389:17 (explaining DTX 375 and DTX 471).)

Besides the Nakagawa Declaration, there is also the Wise Poster, which contains head-to-head comparisons between a coumarin with a propoxy linker and one with a butoxy linker. In the Wise Poster, the butoxy compound did better in both the GBL-induced L-Dopa accumulation assay and the inhibition of spontaneous locomotion behavioral assay that are indicators of antischizophrenic potential in humans. (Castagnoli 672:22-677:3.) Coumarins and carbostyrils are very close in structure. (Bodor Dep. 41:7-9.) The only difference between a carbostyril and a coumarin is that the NH in the carbostyril group is replaced by an O. (Castagnoli 646:3-20.) Coumarins and carbostyrils are "isosters" of each other, which means that they have similar electronic configurations. (*Id.* at 646:3-647:4; Bodor Dep. 41:9-10.) They are expected to have similar chemical, spectral, and reactive properties. (Castagnoli 646:3-20.) In fact, coumarin and carbostyril molecules have nearly identical shapes. (*Id.* at 646:3-25.) Furthermore, the targeted disease in the Wise Poster is schizophrenia. (*Id.* at 652:1-20.) Thus, there was a significant overlap in not only chemistry, but also pharmacology, between the Wise Poster's work on coumarins and Otsuka's work on carbostyrils. (*Id.* at 652:17-20.) Because of the close structural and functional similarity of propoxy coumarins to propoxy carbostyrils, the test results in the Wise Poster on propoxy and butoxy coumarins would have led a skilled person to expect

improvement in going from a propoxy linker to a butoxy linker in carbostyrils. Indeed, the data of the Wise Poster indicates that a butoxy linker is the best of all the options because it is at the maximum point on the parabolic curve for the homologous series of possible linker lengths. (Castagnoli 733:21-735:20.)

Thus, the Nakagawa Declaration and the Wise Poster contain teachings in three different tests (mouse jumping, L-Dopa accumulation, and spontaneous locomotion) indicating that a butoxy linker would yield greater potency than the propoxy linker.

The reexamination examiner allowed the '528 patent solely because she believed Otsuka's argument that an alleged "unexpected" superiority arising from changing from a propoxy to a butoxy linker overcame the strong case of structural obviousness presented by the 2,3-dichloro propoxy compound. The examiner did not, however, know about the Nakagawa Declaration or the Wise Poster. Had she known of either or both of them, she would not have concluded that an improvement upon changing from a propoxy to a butoxy was "unexpected." Without "unexpected" superiority, she would have continued her obviousness rejection. This Court likewise holds the claims invalid for obviousness based on the record in the PTO concerning the 2,3-dichloro propoxy compound, as supplemented by the additional prior art presented by Defendants at trial.

It is the Court's view that this evidence, which refutes the "unexpected" results argument Otsuka made to the PTO, establishes such a strong case of obviousness that it is hard to imagine what possible objective evidence could save the day for Otsuka. *Pfizer*, 480 F.3d at 1372 (strong showing of obviousness not overcome by secondary considerations); *Newell*, 864 F.2d at 768 (Fed. Cir. 1988) (same). In any event, the actual record in this case of purported secondary considerations is unconvincing for the reasons set forth in detail below in Section IV(D)(4).

2. *Obviousness Based on the Unsubstituted Butoxy.*

Claims 12, 17 and 23 of the '528 patent would have been obvious to a person of ordinary skill in the art, over the unsubstituted butoxy compound in view of the prior art. (Press 169:18-173:20.) The unsubstituted butoxy compound, having no substituents on the phenyl ring, is the parent system for aripiprazole. (Press 100:18-100:23.) The Nakagawa Declaration disclosed the unsubstituted butoxy and provided SAR information that would have motivated a person of ordinary skill in the art to modify that compound to make aripiprazole with a reasonable expectation of success in attaining a compound with improved antischizophrenic activity.

a. One of Ordinary Skill in the Art Would Have Selected the Unsubstituted Butoxy as a Lead Compound.

Based on the Nakagawa Declaration, in view of the prior art as a whole, a person of ordinary skill in the art would select the unsubstituted butoxy as a lead compound because it is a 7-linked butoxy compound that can be substituted at the phenyl ring. The Nakagawa Declaration provides Mouse Jumping Test data for nine carbostyril derivative compounds, including the unsubstituted butoxy. (DTX 214 at 14; Press 165:5-166:15.) A medicinal chemist would have focused on 7-linked carbostyril derivatives because the 7-linked compounds OPC-4392 and OPC-4139 were reported to have promising antischizophrenic activity. (Press 164:12-22; Castagnoli 792:3-794:20.) Even though Drs. Roth and Nichols each testified that one of ordinary skill in the art would have chosen the 5-linked compound 44 because it was the most potent, (Roth 1252:3-11; Nichols 1639:22-1640:23), OPC-4392, which had been tested in humans, was a 7-linked compound and a person of ordinary skill would recognize that changing the position on the core could affect activity. (Press 160:19-164:22.) Most importantly, there was nothing in the prior art that would "teach away" from 7-linked compounds because there were no reports of any of them having undesired effects. (Press 166:17-23); *see In re Fulton*, 391 F.3d 1195,

1201 (Fed. Cir. 2004) (explaining that the prior art must suggest something is undesirable; mere disclosure of alternatives does not teach away); *In re Peterson*, 315 F.3d 1325, 1332 (Fed. Cir. 2003) (same)).

The declaration shows that compound 41 (the unsubstituted butoxy) is more potent—ED_{50} of 5.5 mg/kg—than compound 6 (the unsubstituted propoxy)—ED_{50} of 9.3 mg/kg. (Press 134:9-135:15; Castagnoli 671:8-672:7.) The data on these compounds allows a "head-to-head" comparison of the propoxy and butoxy linker, which shows that, all else being equal, the butoxy linker was more potent in the test. Because the butoxy linker made the compound more potent, and it is "the perfect platform to start structure-activity studies" because it is unsubstituted, a person of ordinary skill in the art would have been motivated to select the unsubstituted butoxy as a lead compound. (Press 164:23-166:15.)

b. A Person of Ordinary Skill in the Art Would Have Been Motivated to Modify the Unsubstituted Butoxy Compound to Make Aripiprazole with a Reasonable Expectation of Success.

A person of ordinary skill in the art, with knowledge of OPC-4392, OPC-4139, the '416 patent, the Nakagawa Declaration, and SE '945 would have been motivated to modify the unsubstituted butoxy compound by dichlorinating the phenyl ring. (Press 164:23-168:5.) In doing so, one would arrive at the 2,3-dichloro butoxy compound, aripiprazole, with a reasonable expectation of success in obtaining an antischizophrenic agent with increased potency. (Press 169:3-170:21.)

Starting with the unsubstituted butoxy compound, a person of ordinary skill in the art would have been motivated to use chlorine as a substituent on the phenyl ring based on prior art data from related propoxy compounds. (Press 126:7-127:22; 158:18-159:1; 164:23-166:15; 169:6-171:2.). The Nakagawa Declaration provides SAR data for each of the three mono-chloro

substitutions: compound 43 is the 2-chloro propoxy, compound 39 is the 3-chloro propoxy, and compound 16 is the 4-chloro propoxy. The 4-chloro substitution on the phenyl ring decreased potency to an ED_{50} of 15.1 mg/kg compared to an ED_{50} of 9.3 mg/kg for the unsubstituted propoxy, so a person of ordinary skill in the art would not make a compound with a 4-chloro substitution. The 2- and 3-chloro substituted compounds, having ED_{50} values of 3.3 and 2.5 mg/kg respectively, each significantly increased potency compared to the unsubstituted compound. (Press 164:23-168:5.)

As Dr. Press explained, medicinal chemists operate on the principle that substituent effects that increase potency will be additive—providing the expectation that increased potency from one enhancement will be further increased by another enhancement. (Press 164:23-168:5.) In other words, the person of ordinary skill would expect that a compound with chlorines at both the 2 and 3 positions would result in a compound with increased antischizophrenic potency, because the prior art taught that both the 2-chloro substituted propoxy compound and the 3-chloro substituted propoxy compound showed increased potency over the unsubstituted propoxy compound. (Press 164:23-168:5; Castagnoli 736:12-737:24; DTX 214 at 14.) Since the 4-chloro substituted propoxy compound showed decreased potency compared to the unsubstituted propoxy compound one of skill in the art seeking to increase potency would not make a 4-chloro substitution. Because the propoxy and butoxy compounds are homologs, the person of ordinary skill would expect that they behave similarly, and that a butoxy compound with chlorines at the 2 and/or 3 positions would likewise be more potent than the unsubstituted butoxy. (Press 137:4-138:4; 140:22-142:19; 165:21-166:11; 166:24-168:2); *see In re Dillon*, 919 F.2d 688, 691-92 (Fed. Cir. 1990) (en banc) (explaining that there was a reasonable expectation that two

compositions would have similar properties based on close structural and chemical similarity and the fact that both compounds were used as fuel additives).

In considering the additive effect of a 2,3-dichloro substitution on the butoxy, a person of ordinary skill in the art would have recognized that Otsuka's own Swedish patent application SE '945 reports that a 2,3-dichloro substitution on the phenyl ring of an unsubstituted propoxy compound led to a compound reported to have antischizophrenic activity. (Press 138:8-139:24; 169:20-171:2; DTX 1159-T at 5 and 60-62.) The person of ordinary skill in the art would have been aware of Otsuka's own prior art patent applications (including DE '105 and SE '945), which disclose the 2,3-dichloro propoxy compound, which has chlorines at *both* the 2 and 3 positions of the phenyl ring. (DTX 4 at 16; DTX 1159-T at 60-62; Press 138:8-139:24; 169:20-171:2.) Indeed, SE '945 discloses that the 2,3-dichloro propoxy compound had potential use as an anti-schizophrenic agent. (DTX 1159-T at 5; Press 138:8-139:24; 169:20-170:10; Press 137:8-140:14.)

Moreover, in view of the teachings of the prior art, either the 2,3-dichloro propoxy compound or the unsubstituted butoxy compound render aripiprazole obvious. Taken together, they constitute an even stronger demonstration of obviousness because the 2,3-dichloro propoxy compound and the unsubstituted butoxy compound "bracket" aripiprazole. (Press 101:22-102:18.) *See Payne*, 606 F.2d at 314 ("When prior art compounds essentially 'bracketing' the claimed compounds in structural similarity are all known as pesticides, one of ordinary skill in the art would clearly be motivated to make those claimed compounds in searching for new pesticides.").

c. Conclusion of Obviousness Over the Unsubstituted Butoxy

In sum, a person of ordinary skill in the art would have pursued carbostyril derivatives as antischizophrenic agents, selected the unsubstituted butoxy as a lead compound, and been

motivated to add a 2,3-dichloro substitution to the phenyl ring to arrive at aripiprazole, the compound of claim 12, with a reasonable expectation of success in attaining an improved antischizophrenic agent. (Press 169:18-171:2.) Similarly, a person of ordinary skill would have been motivated to use that compound and a pharmaceutically acceptable carrier together in a composition of claim 17 to treat schizophrenia. (Press 171:15-172:9.) Finally, a person of ordinary skill in the art would have been motivated to treat schizophrenia in a patient using that composition according to the method of claim 23. (Press 172:23-173:20.) Therefore, claims 12, 17, and 23 would have been obvious to a personof ordinary skill in the art in view of the prior art.

3. *Obviousness Based on OPC-4392.*

Aripiprazole also would have been obvious in view of the prior art compound designated by Otsuka as OPC-4392. History reveals that aripiprazole was in fact derived from OPC-4392. (DTX 268-T at OPC 077177 ("OPC-4392, which is the origin of the development of aripiprazole"); DTX 362-T at 1 (It "all started from OPC-4392."), 5 ("I would like to emphasize the importance of the development of OPC-4392 that had served as the basis for OPC-14597 [aripiprazole].").) Prior to the filing of the patent application that issued as the '528 patent, published information about OPC-4392 entered the public domain and became prior art, including what happened with OPC-4392 in Phase I and II clinical trials in humans. Such data about pharmacological activity in humans is particularly noteworthy because schizophrenia is a human disease not known to occur in animals. (Castagnoli 620:13-622:19; Roth 1187:20-24.)

a. OPC-4392 Would Have Caught the Attention of the Hypothetical Person of Ordinary Skill in the Art.

Prior art drug treatment of schizophrenia included the use of drugs such as chlorpromazine and haloperidol that are classed as "typical" antischizophrenic drugs. (Marshall

325:8-326:19; Roth 1128:1-22.) These typical antischizophrenic drugs treat the "positive" symptoms of schizophrenia but not the "negative" symptoms. (Roth 1128:1-22.) Typical antischizophrenic drugs also have problematic side effects, including extrapyramidal symptoms ("EPS"), prolactin elevation (hyperprolactinemia), and sudden decrease in blood pressure (orthostatic hypotension). (Roth 1148:16-1150:5.) Despite these various drawbacks, these typical antischizophrenic drugs are still used today as one of the several options for treating schizophrenia. (*Cf.* PTX 86 (indicating that haloperidol, a typical antipsychotic agent, is still used and that available atypical medications failed to meet the need for an antischizophrenic drug that is better tolerated than earlier typical antischizophrenic drugs).) Clozapine was the first atypical antischizophrenic drug—atypical in the sense that, as compared to the first generation "typical" antischizophrenic drugs, clozapine has much less liability for causing EPS. (Roth 1130:2-9.) It was learned, however, that clozapine can cause a fatal decrease in white blood cells, called agranulocytosis. (*Id.* at 1131:5-25.) Clozapine is still used today, but with careful monitoring of patients that involves frequent blood testing. (*Id.* at 1133:4-21.) In 1988, the desire was to find a drug that would treat both the positive and negative symptoms of schizophrenia, but not cause EPS or agranulocytosis, and otherwise have a good side effect profile. (*See* Press 196:6-18; Castagnoli 642:12-643:12; Roth 1390:15:-1391:2; *cf.* Roth 1530:25-1532:20 (explaining clozapine's lack of EPS but ability to cause significant adverse effects, such as agranulocytosis); Press 152:10-153:10 (explaining that a compound with the ability to treat the negative symptoms would have interested one of skill in the art in 1988).)

OPC-4392 would have caught the eye of the ordinary researcher because the prior art published literature (especially the 1987 Murasaki article, DTX 388-T) reveals that OPC-4392 had a number of very favorable characteristics in humans. First, in clinical tests in humans OPC-

4392 had some activity in ameliorating the positive symptoms of schizophrenia, although it was "not strong" in that regard. (DTX 388-T at 1517; Press 150:24-151:25; Castagnoli 623:11-626:1.) Second, in clinical tests in humans OPC-4392 was particularly strong in relieving the negative symptoms of schizophrenia. (DTX 388-T at 1517; DTX 990; Press 150:24-151:25; Castagnoli 626:16-627:6; 628:16-629:18; 641:2-642:22.) Third, in clinical tests in humans OPC-4392's side effect profile was good with respect to EPS, blood prolactin levels, and orthostatic hypotension. (DTX 388-T at 1517; DTX 874; DTX 990; Press 153:22-156:1; Castagnoli 627:7-627:23; 639:24-640:9, 641:2-642:2.) There was also no indication that agranulocytosis would develop. (Castagnoli 911:13-912:9.) Sometimes there were side effects such as nausea, but these were not life threatening and did not prevent its administration to humans. (DTX 388-T at 1517; Press 154:20-156:1; Castagnoli 627:24-628:15.) In short, OPC-4392 had all the characteristics researchers sought in an antischizophrenic drug, save only that its effect on positive symptoms was "not strong." (Press 150:25-156:1.)

In 1988, a typical research team looking at the publicly reported results of the clinical trials in humans would have concluded that a carbostyril similar to OPC-4392 would likely have the characteristics desired in an antischizophrenic drug. (Castagnoli 642:12-18.) This typical research team would have continued to pursue this line of research by selecting for further testing a group of compounds that were variations on the OPC-4392 theme. (Castagnoli 642:19-643:12.) Such research usually involved testing a group of compounds, rather than proceeding one compound at a time. (Castagnoli 800:24-801:13.) The question the typical research team would have faced is what changes should be made to OPC-4392's structure so as to increase potency without losing the compound's advantages that had been demonstrated in human trials. (Castagnoli 644:7-23.)

b. The Typical Research Team Would Not Have Abandoned Carbostyrils.

Otsuka contends that OPC-4392 was such a complete failure that all carbostyrils would have been abandoned as candidates for an antischizophrenic drug. There are several problems with Otsuka's position.

To begin with, if accepted, Otsuka's contention would end up invalidating the '528 patent under 35 U.S.C. § 101 (utility requirement) and § 112 (how to use requirement). If the human tests on OPC-4392 had been such a failure as to discourage further work on carbostyrils, then the '528 patent would not contain sufficient evidence to change the outlook for carbostyrils. This arises from the fact that human trials trump animal studies. (Kikuchi Dep. 98:25-99:15; Marshall 613:22-614:119; Castagnoli 621:10-20.) The '528 patent has test results from just one animal study that even arguably correlates to antischizophrenic potency, and no data at all from humans. (Nichols 1726:20-1727:23.) Thus, if it were true (it is not) that the prior art taught away from using carbostyrils to treat schizophrenia, then the '528 patent would be invalid under §§ 101 and 112 because the patent lacks a sufficient scientific basis to convince a skeptical reader that aripiprazole would successfully treat schizophrenia where other carbostyrils would not. *Eli Lilly & Co. v. Actavis Elizabeth LLC*, No. 07-CV-3770 (DMC)(JAD), 2010 WL 3210516, at *27-40 (D.N.J. Aug. 12, 2010) (holding patent invalid for lack of enablement/utility because "a person of ordinary skill would not have recognized the method of treatment's utility in view of the specification and prior art").

The evidence also refutes Otsuka's argument. OPC-4392 is entirely different from the list of failures presented by Prof. Nichols. (Nichols 1719:6-1721:20.) Unlike OPC-4392, those failures did not treat negative symptoms of schizophrenia. (*Id.* at 1721:3-8.) Those failures suffered from various side effects that OPC-4392 did not have. (*Id.* at 1721:9-20.) Rather than

classifying OPC-4392 as a failure, both public and internal Otsuka documents recommended that further work be devoted to OPC-4392. (DTX 362-T; Roth 1413:10-1414:15; 1419:10-14; *see* DTX 388-T at 5 (noting that OPC-4392 "shows promise" and that its "clinical effects are expected to differ from conventional antipsychotics"); DTX 394 at OPC0767398 ("This hypothesis should be confirmed in further studies."); DTX 322-T at 1 ("Phase III clinical trials are currently being conducted on OPC-4392, with the aim of applying for it as a drug for treating schizophrenia."); Oshiro 1803:21-1805:14.) In an article published in 1993, researchers in Europe still classified OPC-4392 as a "promising alternative in the treatment of schizophrenic syndromes." (DTX 396 at 180; Roth 1421:20-21 ("They're classifying it as a promising alternative, yes.").) While this article is too late to be considered by the hypothetical skilled person in 1988, it is evidence of how skilled persons actually did evaluate OPC-4392's potential only a few years later and, therefore, corroborates the conclusion that OPC-4392 was not an abject failure to be ignored.

Otsuka now asserts that OPC-4392 had no activity with regard to the positive symptoms of schizophrenia. What the 1987 Murasaki article (DTX 388-T) actually says is that OPC-4392 was "not strong," which implies some activity. (Castagnoli 625:13-626:1.) If there had been no activity at all, it would have said that instead. Indeed, Otsuka's own internal reports state that OPC-4392 was "weak" on the positive symptoms, and *not* that it was without any activity at all. (PTX 34-T at OPC0768534; DTX 59-T at OPC0717008.) While the hypothetical skilled person would not know of these internal documents, the statements in these documents corroborate the common sense reading of the prior art 1987 Murasaki article's use of the language "not strong" to mean some activity. Furthermore, the 1987 Murasaki article did not recommend abandoning OPC-4392, but rather invited further research by saying that "there is anticipation for the

treatment of the chronic stages of schizophrenia." (DTX 388-T at 1517.) Otsuka's after-the-fact, litigation-induced argument that carbostyrils would have been abandoned is, therefore, refuted by information from the relevant time period. The skilled person would not have concluded that OPC-4392 could not be upgraded. *KSR*, 550 U.S. at 425 ("What the declaration does not indicate is that Asano was somehow so flawed that there was no reason to upgrade it . . . ."). Rather, she would have concluded that all OPC-4392 needed was additional potency for treating the positive symptoms of schizophrenia, and the prior art suggested how to do that.

c. How the Typical Research Team Would Have Proceeded to Optimize OPC-4392.

One of the very first things a typical research team would have considered doing with OPC-4392 is to change the length of the linker by adding or subtracting a link. Compounds that differ only by the number of links in a chain are called homologs of each other, and "[t]he simplest change that can be made is . . . to investigate the pharmacology of a homologous series." (DTX 1012 at 306.) So the typical research team would have immediately considered changing the length of the linker. As already discussed in Section III(G)(3), the prior art test data in the Nakagawa Declaration and the 1987 Wise Poster suggest adding one more linking carbon so as to go from a "propoxy" linker to a "butoxy" linker.

As already discussed in Section III(G)(3), one of ordinary skill would have immediately thought of chlorine as a substituent candidate on the phenyl ring. Chlorine is about the same size as methyl and would, therefore, not have been seen as a big structural change. (Castagnoli 739:23-740:16.) The prior art 1987 Wise Poster contains a head-to-head comparison between a propoxy coumarin with a *chlorine* substituted at the 3-position and a propoxy coumarin with a *methyl* substituted at the 3-position. (Castagnoli 737:25-739:22.) In each of three different tests for the suppression of dopamine activity, which is an indicator of antischizophrenic potential, the

chlorine was more potent than the methyl. (*Id.*) That would have been a very strong suggestion to substitute chlorine for methyl in OPC-4392 in order to improve its antischizophrenic potency.

OPC-4392 was a *double* bonded carbostyril. (Castagnoli 659:6-660:5.) All nine of the compounds in the Nakagawa Declaration's report of mouse jumping test results were *single* bonded carbostyrils. (Castagnoli 662:3-663:11.) The coumarins in the 1987 Wise Poster are all *double* bonded. (*Id.*) In view of this mixture of single and double bonded compounds in the prior art, and the absence of any head-to-head studies comparing single and double bonds, the typical research team would not have picked between these two alternatives. (Castagnoli 662:6-663:11.) The typical research team would instead have made both versions of each compound. (*Id.*) This approach is suggested by the '416 patent's disclosure of about 250 pairs of single and double bonded carbostyril compounds.[15] (DTX 6; Castagnoli 665:4-11.)

In view of the foregoing, the typical research team would have gone forward to develop a group of compounds that included (1) changing from a propoxy to a butoxy linker, (2) substituting chlorine for methyl on the phenyl ring, and (3) using single bonds and double bonds in the carbostyril as alternatives. Prof. Castagnoli, a medicinal chemistry expert, testified that there would have been eight compounds in this group. (Castagnoli 797:15-801:13.) This group would have included aripiprazole. (Castagnoli 797:15-804:11.)

From making these changes, the person having ordinary skill in the art ("PHOSITA") would have reasonably expected that the modified compounds in this group would have increased potency compared to the prior art and a good side effects profile.

[15] Although the hypothetical skilled person could not know it in 1988, subsequent events would reveal that in the body aripiprazole metabolizes into its double bonded counterpart and that this metabolite contributes to the drug's activity. (DTX 564 at 57 § 12.3; Nichols 1733:21-1735:2.) The '528 patent itself claims both the single and double bond versions. (Nichols 1728:10-1730:21.)

Q. So bottom line, what would the PHOSITA take away from the Nakagawa declaration and the Wise poster with regard to this issue of the linker length?
A. Right. So she had three clear teachings: The binding data, the locomotion data, and the jumping data. Maybe we didn't make that clear. That Nakagawa table was reporting on Inhibition of Mouse Jumping. She had three clear statements that butoxy is a more potent compound than propoxy in assays which are relevant to the antipsychotic potential of these molecules.
Q. So what would she do?
A. She would have done the same thing that she would have done from the information of Nakagawa. She would have increased the chain length in her series of compounds from propoxy to butoxy.
Q. And what would she expect to get?
A. She would have expected to get just what she's trying to get. That's her expectation. This is supporting her expect -- enhancement in the antipsychotic activity of the resulting molecule.

* * *

Q. What would the PHOSITA in '88 expect from these compounds; what kind of properties?
A. Yes. So she was -- the PHOSITA would expect that these compounds would show enhanced activity going down the list. That is, the compound at the top would be less potent. And when I say "activity," I'm referring to antidopaminergic activity, antipsychotic activity, potential antipsychotic activity.

Replacement of one methyl with chloro or this methyl with chloro would lead to compounds with enhanced activity, and replacement of both methyls with chloro would lead to the most active compound.

* * *

THE WITNESS: May I add one additional comment?
THE COURT: Sure.
THE WITNESS: The additional comment is to appreciate the outstanding exception in terms of human pharmacology that was reported in the clinical studies. That is, what 4392 lacked was this antipsychotic component.

So the PHOSITA is focused on that issue, but she's pretty smart because she doesn't depart from 4392 in any

> significant way. She stays close to home.
> BY MR. CHERRY:
> Q. And because she stays close to home, what does she expect with regard to EPS?
> A. All right. She expects in staying close to home that those side effects, not only EPS but the others, the hyperprolactinemia and the orthostatic hypotension, which are -- and there's one we haven't talked about, target dyskinesias, which is a very serious outcome of typical neuroleptics -- would not be part of the side effect profile of these compounds. That's her anticipation, her expectation.
>
> * * *
>
> From the changes that she would have made, she would have expected that those new compounds would treat positive symptoms more effectively than 4392. And because the compounds are structurally very similar to 4392, she would have expected that those analogs would not have lost the attractive properties of treating negative symptoms, no toxicity, and good side effect profile.

(Castagnoli 677:4-23; 801:14-25; 803:9-804:3; 816:16-22.) Of course these compounds would have to have been tested to determine their properties, but that does not avoid obviousness because only a reasonable (not absolute) expectation of success is required.

> We cannot reject the district court's finding that in 1986, it was generally unpredictable as to whether a particular salt would form and what its exact properties would be. The problem with the district court's ultimate conclusion of non-obviousness based on that factual finding, however, is that case law is clear that *obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success*. . . . Indeed, a rule of law equating unpredictability to patentability, applied in this case, would mean that any new salt--including those specifically listed in the '909 patent itself—would be separately patentable, simply because the formation and properties of each salt must be verified through testing. This cannot be the proper standard since *the expectation of success need only be reasonable, not absolute*.

Pfizer, 480 F.3d at 1364 (emphasis added) (citing *In re Corkill*, 771 F.2d 1496, 1500 (Fed. Cir. 1985)); *see also Biocraft*, 874 F.2d at 809 ("But, 'absolute predictability of success' is not the

criterion; '[f]or obviousness under § 103, all that is required is a reasonable expectation of success.'") (quoting *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988); *Longi*, 759 F.2d at 897 ("Only a reasonable expectation of success, not absolute predictability, is necessary for a conclusion of obviousness."). The evidence demonstrates a more than reasonable expectation of success. (Press 168:23-169:2 ("I don't think anyone can predict 100 percent of anything. But in this regard no, we can't predict, but we have a high expectation that that would be the right thing to do and would be very successful.").) Each member of this group, including aripiprazole, would therefore have been obvious to a person of ordinary skill in the art in October 1988.

Defendants do not have to prove that aripiprazole was the only obvious choice or the best choice, only that it was one of the obvious choices. *Fulton*, 391 F.3d at 1200 (Obviousness does not require that the claimed invention be the "preferred, or most desirable" choice.); 1201-02 (It is legal error to rely on "the mistaken premise that the prior art must teach that a particular combination is preferred, or 'optimal,' for the combination to be obvious."); *Carter-Wallace*, 474 F.2d at 543 ("[A] development cannot be regarded as unobvious simply because it was not the first, or even the second or third, structural change of which a researcher would think."). For example, in *Merck & Co. v. Biocraft Labs.*, 874 F.2d 804, 807 (Fed. Cir. 1989, the obviousness of the claimed drug formulation was not negated by the fact there were over a thousand others that were also obvious.

> [T]he [prior art] '813 patent instructs the artisan that any of the 1200 disclosed combinations will produce a diuretic formulation with desirable sodium and potassium eliminating properties.
>
> That the [prior art] '813 patent discloses a multitude of effective combinations *does not render any particular formulation less obvious*.

874 F.2d at 807 (emphasis added).

Otsuka contends that the prior art suggests that other changes be made to OPC-4392. The typical research team could have gone ahead and made Otsuka's suggested changes as well as the ones discussed above. That would have resulted in a more numerous group of test compounds, but still would have included aripiprazole in the group. All those compounds would have been obvious in October 1988. *Fulton*, 391 F.3d at 1200 (obvious even if not the "preferred" combination), 1201-02 (same); *Carter-Wallace*, 474 F.2d at 545 (Claimed invention held obvious even though it was not "the preeminent suggestion of the art or the evident first choice of the investigator."). The number would still have been far fewer than the 1,200 combinations that were all regarded as obvious in *Biocraft*, 874 F.2d at 807. For example, Otsuka argues that the prior art suggests changing the attachment point between the carbostyril group and the linker from the 7 position to the 5 position. Both Dr. Press and Prof. Castagnoli testified about why the skilled person would have made other modifications before undertaking to change the linker attachment position. (Press 159:8-164:10, 162:8-164:10; Castagnoli 793:19-794:20.) Even if that option were added to the group of compounds to be tested by the person of ordinary skill, that would add 8 more compounds to bring the total to 16 compounds. (Castagnoli 805:21-23.) That would still result in the obviousness of the entire group, including aripiprazole.

4. *The Evidence Pertaining to Objective Indicia of Nonobviousness.*

Although the ultimate burden of proof of invalidity is on the accused infringer, the burden of going forward with rebuttal evidence shifts to the patentee once the challenger has presented a prima facie case of invalidity. *Pfizer*, 480 F.3d at 1360; *Bally Gaming, Inc. v. IGT*, 623 F. Supp. 2d 1213, 1220 (D. Nev. 2008), *aff'd*, 335 F. App'x. 48 (Fed. Cir. 2009); *Optivus Tech., Inc. v. Ion Beam Applications S.A.*, No. CV 03-2052 SJO, 2005 WL 6070811, at *15 (C.D. Cal. Mar. 14, 2005), *aff'd*, 469 F.3d 978 (Fed. Cir. 2006). In this case the evidence under

the prior art and level of skill factors of the *Graham* analysis is more than sufficient to establish obviousness unless there is additional evidence pointing towards nonobviousness, and so Defendants have established a prima facie case. Accordingly, Otsuka has the burden of production regarding the objective indicia of nonobviousness (a/k/a secondary considerations). *Id.*

a. Alleged "Unexpected" Superiority.

Otsuka contends that obviousness is negated by alleged "unexpected" superiority of aripiprazole. While unexpected superiority, when proved, is a factor to be considered, it is not sufficient to overcome a strong case of obviousness. *Pfizer*, 480 F.3d at 1372-73. In order for alleged unexpected results to be probative of nonobviousness, it must be proved that "there actually is a difference between the results obtained through the claimed invention and those of the prior art," and that "the difference actually obtained would not have been expected by one skilled in the art at the time of invention." *In re Freeman*, 474 F.2d 1318, 1324 (C.C.P.A. 1973) (citations omitted). In this case Otsuka did not demonstrate unexpected superiority over the relevant prior art, on which issue it has the burden of presenting evidence. *Pfizer*, 480 F.3d at 1371-72.

(1) Otsuka's Internal Data Indicate That Aripiprazole Does Not Have Unexpectedly Superior Antipsychotic Potency.

Using the Hirose Declaration, Otsuka asserts that aripiprazole has unexpectedly superior potency in a test said to correlate to antischizophrenic activity. The Hirose Declaration results, however, do not demonstrate unexpected results because they are inconsistent with internal Otsuka test results, not reported to the PTO, that indicate that the difference in potency between aripiprazole and the 2,3-dichloro propoxy is not unexpected.

The test results reported to the PTO in the Hirose Declaration purport to show that aripiprazole is 23 times more potent than the prior art 2,3-dichloro propoxy compound in the anti-apomorphine stereotypy test. (Oshiro 1902:24-1903:7.) The alleged unexpected superiority of aripiprazole over the 2,3-dichloro propoxy is, therefore, based on the *degree* of antipsychotic potency. There are internal Otsuka test results, not reported to the PTO, that show that the difference in potency was much lower. In Dr. Oshiro's 1987 year-end presentation to Otsuka, the 2,3-dichloro propoxy had an anti-apomorphine stereotypy ED_{50} value of 2.5 mg/kg and aripiprazole had an anti-apomorphine stereotypy ED_{50} value of 0.4 mg/kg. (DTX 59-T; Oshiro 1821:14-23; Oshiro 1900:24-1901:7; 1821:1-8; 1901:8-20.) These internal ED_{50} values indicate only a six-fold difference in potency between the 2,3-dichloro propoxy and aripiprazole. (Oshiro 1902:24-1903:7.) Dr. Oshiro testified that a six-fold difference in potency between a propoxy compound and a butoxy compound was not unexpected. (Oshiro 1772:12-1773:3; 1843:21-1845:9; PTX 35-T.) In particular, on direct examination Dr. Oshiro testified that improvement in anti-apomorphine stereotypy potency that he observed when changing the propoxy linker of OPC-4392 to a butoxy linker was neither considerable nor surprising. (Oshiro 1772:12-1773:3) On cross, Dr. Oshiro noted that that difference was six fold. (Oshiro 1843:21-1845:9; PTX 35-T.) Otsuka offered no explanation for this discrepancy between Otsuka's internal data and the data presented in the Hirose Declaration. The Hirose Declaration, therefore, does not demonstrate that aripiprazole has unexpectedly superior potency as compared to the 2,3-dichloro propoxy.

Further, Otsuka's internal documents show that the prior art 2,3-dichloro propoxy compound got good scores in the anti-apomorphine stereotypy and anti-epinephrine lethality tests. (DTX 59-T at OPC 0717014; Oshiro 1821:16-25.) For example, it did better than the

known antischizophrenic drug chlorpromazine in both the anti-apomorphine stereotypy and anti-epinephrine lethality tests. (*Id.*) The record indicates that the 2,3-dichloro propoxy compound was held back from commercialization by Otsuka, not because of its properties, but rather because it could not be patented due to its disclosure in the prior art SE '945 patent application. (Oshiro 1822:9-1827:16.) On such a record, one cannot assign patentable superiority to aripiprazole.

(2) The Hirose Declaration Results Are Uninterpretable and Thus Do Not Support Otsuka's Claim of Unexpected Results.

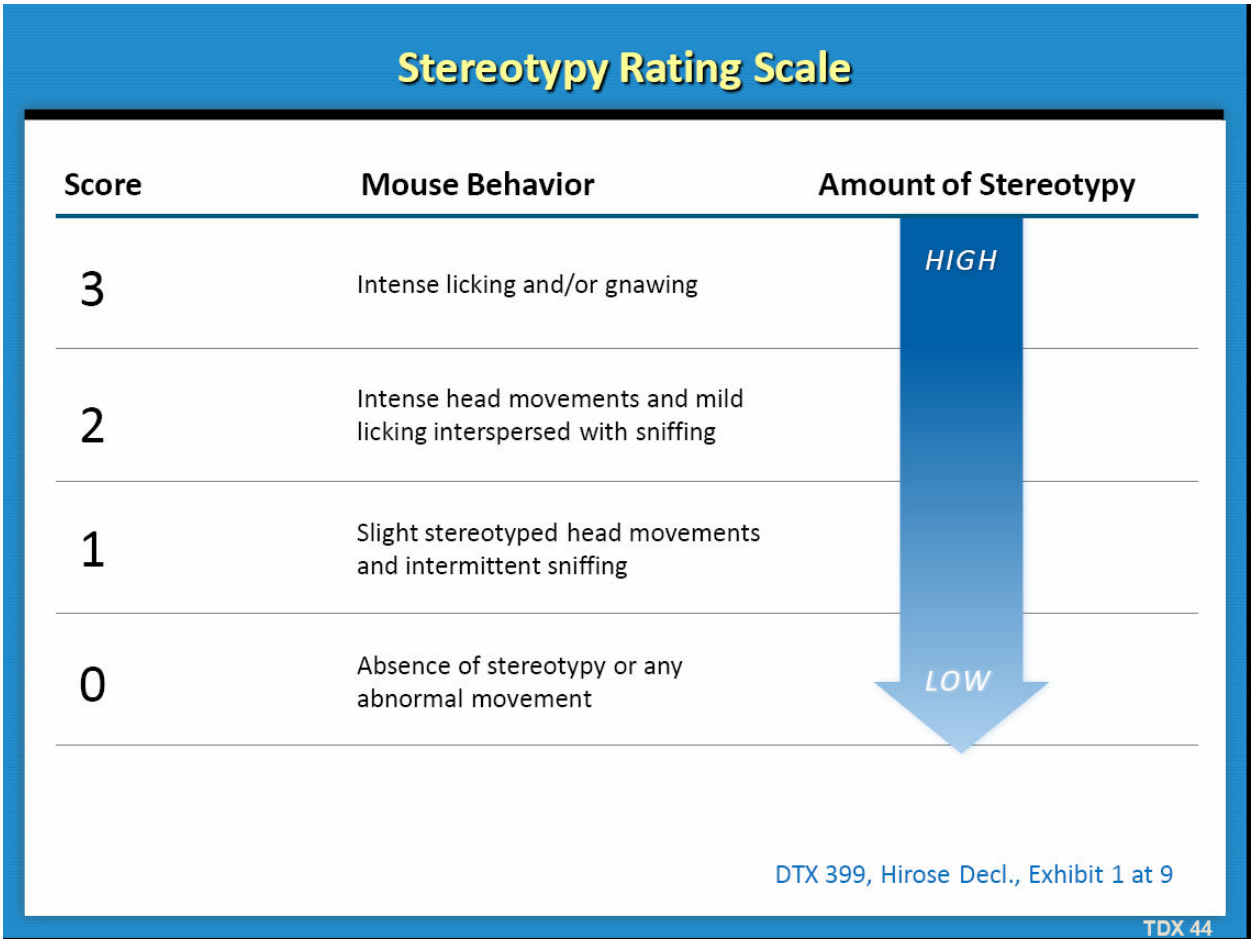
In addition to being inconsistent with Otsuka's internal data, the Hirose Declaration results cannot prove unexpected superiority of aripiprazole over the 2,3-dichloro propoxy compound because they cannot be meaningfully interpreted. There are two issues with the testing reported in the Hirose Declaration that render the results uninterpretable. The first issue is the existence of a confound because two observers scored the test mice in a manner that made it impossible to know whether the differences in scores were due to the observer or the test compound—*i.e.*, one observer scored all of the aripiprazole test mice and the other scored all of the 2,3-dichloro propoxy test mice. The second issue is possible bias because the observers scoring the mice were not blinded to the identity of the compounds being tested.

(a) The Hirose Declaration Data Are Confounded.

The data in the Hirose Declaration cannot be meaningfully interpreted because of a confound inherent in the test methodology. A confound exists when two variables change systematically together. (Beninger 938:1-10.) In this case, the two variables were the observers, Drs. Hirose and Kikuchi, and the test compounds, aripiprazole (compound 1) and the prior art 2,3-dichloro propoxy (compound A). (*Id.*) Dr. Hirose scored all of the mice in the group given aripiprazole, and Dr. Kikuchi scored all of the mice in the group given the 2,3-dichloro propoxy

compound. (*Id.*) The test compounds could vary by virtue of being different compounds. The different observers could vary by virtue of making different judgments using the scoring scale, which was subjective.

The confound problem is rooted in the fact that the anti-apomorphine stereotypy test is scored using a subjective scale. (Beninger 938:15-939:20; 940:10-942:18; DTX 537; DTX 411; DTX 529.) The test is subjective because the observer must make an individual judgment as to which level on a scoring scale an animal's behavior falls into. (Beninger 938:15-939:20.) The scoring scale used for the testing in the Hirose Declaration is illustrated as follows.



(TDX 44 (citing DTX 399, Ex. 1 at 9).) The reason why this scale is subjective is that it requires the observer not only to judge *whether* an animal exhibits stereotyped behaviors, but also to

assess the *intensity* of the behaviors being observed. (DTX 411 at 253; Beninger 939:18-20.) An observer using this scale must judge, for example, "mild" versus "intense" licking to choose between a rating of 2 and a rating of 3. (Beninger 938:15-939:20.) Similarly, an observer must make a distinction between "intermittent sniffing" and "sniffing" to distinguish between a rating of 1 and a rating of 2. (*Id.*) Dr. Roth's testimony that the scale is "an objective score because we're not asking the mouse to tell us what their degree of stereotypy is," is not credible. (Roth 1116:17-19.) The subjective nature of stereotypy rating scales was recognized in the art. (Beninger 940:10-942:18; DTX 537; DTX 411; DTX 529.)

The confound occurs because there were two different observers scoring two different compounds on a subjective scale, and the scores for the compounds were then compared. (Beninger 943:14-20.) The concern is that the observers themselves may have differed in how they scored the stereotypy. (*Id.*) Any differences in the scores could be attributed to a difference in the effects of the compounds or a difference in the judgments of the observers. (*Id.* at 938:1-10.) Moreover, a statistical analysis between the two observers for the zero dose control groups cannot eliminate the confound because the confound is inherent in the methodology and thus inextricable. (*Id.* at 943:25-944:18; 945:21-946:17.) The statistical analysis done by Otsuka's expert, Dr. Thisted, showing no significant difference in how observers rate the mice at the zero dose does not alleviate concerns about the confound. (Beninger 945:25-946:17.) Because the zero dose group does not receive the test compound, it presents only one variable—the observer. (Thisted 1482:16-1483:8.) However, that group would exhibit maximum stereotypy and one would expect the observers' agreement to be good. Because of the confound inherent in the methodology, there is no data to establish whether there is agreement between observers when

observing treated animals at the varying doses of test compounds, which calls for more difficult judgments. (Beninger 943:25-945:6.) As Dr. Beninger explained:

> Q. And would a statistical analysis showing statistical consistency between the two raters for the control group of mice eliminate the compound?
> A. No.
> Q. Why not?
> A. Well, it's possible that when animals are showing quite strong stereotypy, as the control animals would, not having been treated with any compound, that the raters' agreement is fairly good.
> But as the compounds begin to take effect, and they move through the rating scale and are making judgments between 3 and 2, and 2 and 1, and 1 and 0, it's possible that they still differ in when they identify those transitions between levels.
> Q. And when you say "they," you're talking about the two raters?
> A. Correct.
> Q. And how they would actually make that rating?
> A. Yes.
> THE COURT: And you're saying full-blast apomorphine might be more overt behavior that would be more -- would be less subjective to observe, and as the effect of your compound settles upon the animal, then the behavior changes at different rates?
> THE WITNESS: The judgment of how it changes is more difficult, perhaps.
> THE COURT: Because this behavior is not quite as pronounced --
> THE WITNESS: Yes.
> THE COURT: -- as it was in the beginning?
> THE WITNESS: Because there are only elements of it left, yes.

(Beninger 943:25-945:6.) Dr. Roth's testimony that he "recalculated the curves and they seemed just fine," and that he "looked at" the curves and "failed to find any evidence . . . which would indicate any sort of confound," is unpersuasive because a confound is inherent in the methodology. (Roth 1125:19-23; 1110:1-4; Beninger 945:21-946:1.) Therefore, the Hirose

Declaration data cannot persuasively evidence unexpected results because the confound inherent in its protocol renders the results uninterpretable.

(b) The Hirose Declaration Results Are Potentially Biased.

The Hirose Declaration stereotypy test results are potentially biased, and therefore unreliable, because the observers were not blinded to the identity of the test compounds. As Dr. Beninger testified, "[e]xperimenter bias can occur when . . . somebody doing the rating or scoring has an expectation of the outcome." (Beninger 946:23-947:4.) An expectation of the outcome "can consciously or unconsciously influence the decisions made by an individual." (*Id.*) Here, Drs. Hirose and Kikuchi were not blinded to the identity of the test compounds, and therefore knew which mice were in the aripiprazole test group and which mice were in the prior art 2,3-dichloro propoxy compound test group. (Thisted 1471:2-4; Hirose 1986:8-14.) Thus, conscious or unconscious bias could have been present when Dr. Hirose and Dr. Kikuchi scored stereotyped behavior because the expectation could result in shifting between scores at the transitions—*e.g.*, a score of 2 to a score of 1. (Beninger 947:25-13; 955:2-10.)

Moreover, blinding the observers to the dose of test compound that the mice received would not eliminate the potential bias. (*Id.* at 955:2-20.) Dr. Roth opined that the protocol was a "perfectly acceptable" way to do the experiment. (Roth 1107:8-1108:25.) However, this methodology still allows for potential bias because the observers' knowledge about the identity of the test compound could still affect their judgments and cause shifting between scores at the transitions, and it would have been easy to avoid this flaw. (Beninger 955:2-20.) Neither Dr. Roth's nor Dr. Thisted's analyses of the data could eliminate concern over potential "systematic bias in the data" because systematic bias could affect the entire curve and the control dose would not reveal the effects of bias at the scoring transitions. (*Id.*; Roth 1115:22-25; Thisted 1462:12-

1463:13.) Therefore, the potential for bias makes it impossible to draw any reliable conclusions from apomorphine-induced stereotypy results in the Hirose Declaration. (Beninger 957:7-11.) Thus, the Hirose Declaration stereotypy results cannot prove that aripiprazole's antipsychotic potency is unexpectedly superior to the potency of the prior art 2,3-dichloro propoxy compound. (DTX 399 ¶ 15.)

(3) Even If the Hirose Declaration Demonstrated That Aripiprazole Had Increased Antipsychotic Potency, That Increased Potency Would Have Been Expected.

As set forth above, Otsuka cannot use the flawed Hirose Declaration to demonstrate that aripiprazole has unexpectedly superior antipsychotic potency to the closest prior art compounds. Even if one were able to conclude that aripiprazole had increased antipsychotic potency, that increased potency would have been *expected* based on the prior art Nakagawa Declaration and Wise Poster. The evidence does not establish that the "claimed [compounds] possess unexpectedly improved properties or properties that the prior art does not have." *Dillon*, 919 F.2d at 692-93.

The Court must first consider "what properties were expected." *Pfizer*, 480 F.3d at 1371; *accord In re Mageli*, 470 F.2d 1380, 1384-85 (C.C.P.A 1973) ("Unobviousness, however, cannot be predicated on superiority alone. Obviousness depends on what those skilled in the art would *expect*.") (emphasis in original). Whether a particular property is unexpectedly superior is determined in the context of a person of ordinary skill in the art. *In re Geisler*, 116 F.3d 1465, 1469 (Fed. Cir. 1997). As explained above, based on the Nakagawa Declaration (DTX 214) and Wise Poster (DTX 398), one of skill in the art would have expected improved antipsychotic potency in changing from a propoxy linker to a butoxy linker. *See Aventis*, 499 F.3d at 1302 (finding increased potency alone insufficient absent a showing that the results were unexpected); *In re Gershon*, 372 F.2d 535, 538-39 (C.C.P.A. 1967) (finding results expected based on the

prior art teachings). Thus, aripiprazole's improved antipsychotic potency does not qualify as evidence of "unexpected" superiority because that would have been expected, not unexpected.

(4) Otsuka Did Not Offer Other Evidence Establishing That There Is an Actual Difference in Properties Between Aripiprazole and the Closest Prior Art.

Otsuka has not performed the head-to-head comparisons needed to demonstrate that there are any actual differences in properties between the relevant prior art and aripiprazole. For example, Otsuka relies on Dr. Roth's "Heat Map," but that map presents no data at all regarding the 2,3-dichloro propoxy compound, the unsubstituted butoxy compound, or OPC-4392. (Roth 1329:18-1331:4.) Otsuka also points out that, unlike other atypical antischizophrenic drugs, aripiprazole has been approved for use for treatment of not just schizophrenia, but also for add-on treatment for major depressive disorders, for certain aspects of Bipolar I Disorder, and for treatment of irritability associated with autistic disorder in pediatric patients. (Jarosz 2006:15-2007:6.) Otsuka's arguments are beside the point because Otsuka's comparisons are being made to other approved atypicals and *not* to the *closest prior art* (*e.g.*, the 2,3-dichloro propoxy compound). *See In re Baxter Travenol Labs*., 952 F.2d 388, 392 (Fed. Cir. 1991) (comparison must be made to closest prior art); *accord In re Johnson*, 747 F.2d 1456, 1461 (Fed. Cir. 1984); *Mageli*, 470 F.2d at 1385.

Otsuka has presented no evidence on which the Court can base a finding that the relevant prior art *carbostyrils* do not also have the ability to treat additional conditions such as bipolar disorder. *See, e.g.*, *Freeman*, 474 F.2d at 1324 (Applicant must show "that there actually is a difference between the results obtained through the claimed invention and those of the prior art." (citations omitted)); *Susi*, 440 F.2d at 446 ("[T]o overcome a finding of prima facie obviousness by establishing that the claimed compositions are superior to what one of ordinary skill in the art would expect, it was up to appellant to bring forward reasonable evidence concerning the light-

stabilizing properties of the prior art as well as concerning the light stability of the claimed compositions.").

Even if a claimed compound has "unexpected" properties, that does not show nonobviousness unless it is also shown that the relevant prior art compounds do not in fact share those properties.

> Appellant attempts to overcome this prima facie case of obviousness by arguing the following:
>
> > Even if said references sufficed to render obvious the structure of appellant's compounds, they, as a matter of law, would not render obvious the compounds themselves *(and all the properties that inhere therein)* under 35 USC 103; for the herbicidal utility of these compounds is contraindicated by these references. [Citations omitted.]
>
> Reflection on this contention shows it to be appellant's position that if his compounds possess an advantageous *property* which is unobvious (unexpected) in view of the disclosures of the prior art references, then the prima facie case of obviousness necessarily has been overcome and his *compounds* must be held to be unobvious. None of the cited cases, however, explicitly or implicitly supports this proposition. In each, a prima facie case of obviousness was conceded or held to have been established and applicant's proofs, submitted to overcome that prima facie case, related not merely to *unexpected* properties, but rather to unexpected *differences* in properties, i.e., to *actual* differences in the properties of the prior art compounds and the properties of the compounds involved in the appealed claims. Such actual differences in properties are required to overcome a prima facie case of obviousness because the prima facie case, at least to a major extent, is based on the expectation that compounds which are very similar in structure will have similar properties. Therefore, to *overcome* the prima facie case, it must be shown that the expectation on which it is based was in fact unsound—*as* by showing that there are substantial, actual differences in properties.
>
> Inasmuch as the record here is silent as to how the reference compounds and the claimed compounds actually differ in properties*, if at all*, appellant has failed to overcome the examiner's prima facie case of obviousness.

In re Hoch, 428 F.2d 1341, 1343-44 (C.C.P.A. 1970) (italics in original) (underlining added) (footnotes omitted) (citations omitted) (obviousness affirmed).

> Although appellant's evidence shows a substantial difference in skin toxicity between the claimed compound and the isomer, the evidence does not

> point out a single *actual* difference in properties between the claimed compound and the homologue. Wilder's discovery of the absence of skin toxicity in the claimed compound does not end the inquiry, because one who claims a compound, per se, which is structurally similar to a prior art compound must rebut the presumed expectation that the structurally similar compounds have similar properties. *In re Hoch*, supra. Appellant has shown no *actual difference* in properties between the two compounds or any other evidence sufficient to rebut that expectation.

Wilder, 563 F.2d at 460 (italics in original) (underlining added) (obviousness affirmed).

Besides the usual presumption that compounds with similar structures have similar properties (*Wilder*, 563 F.2d at 460; *Hoch*, 428 F.2d at 1344), there is in this case evidence indicating prior art carbostyril derivatives likely have properties similar to aripiprazole. For example, the '416 patent states that its compounds are useful as, *inter alia*, "antimanic-depressive agents" (*i.e.*, useful in treating bipolar disorder). (DTX 6 at 3:17-18; Roth 1220:13-1221:9; Jarosz 2110:18-2112:2.) In any event, it was up to Otsuka to present evidence that aripiprazole and the closest prior art had different properties (*Wilder*, 563 F.2d at 460; *Hoch*, 428 F.2d at 1344), even if at the time of the invention it was unknown whether the closest prior art had such properties. *Baxter*, 952 F.2d at 392 ("latent properties in the prior art . . . unknown at the time") (citation omitted). Thus, Otsuka's entire approach to unexpected results is flawed because it fails to establish that aripiprazole in fact differs from the relevant prior art compounds.

(5) Otsuka's Blocking Patents Sever Any Nexus Between the '528 Patent Claims and Unexpected Properties.

The relevance of evidence of alleged unexpected superiority to an obviousness analysis is based on the inference that "if others in the art could have come up with a product" having the allegedly superior property, "they certainly would have done so." *In re D'Ancicco*, 439 F.2d 1244, 1248 (C.C.P.A. 1971). That inference cannot be drawn here because Otsuka's extensive patent position discouraged others from working in the carbostyril derivative field.

Otsuka's several prior art patents on carbostyril derivatives laid claim to an enormous number of compounds. (*See* DTX 6; DTX 20; DTX 248-T; DTX 1159-T.) The '416 patent alone covered at least nine trillion compounds. (Nichols 1624:8-12; 1716:17-1717:2.) The '416 patent therefore removed that entire class of compounds from the public's hands. (Press 116:14-117:5; Roth 1241:9-22; Nichols 1624:8-1626:3.) This eliminated any incentive for persons in the field of antischizophrenic drug research to pursue carbostyril compounds. Dr. Press explained the situation as follows:

> [P]harmaceutical companies do this because they hope to make a drug out of it to make money.
>
> If they have their scientific staff looking at a drug or drug candidate that's owned by somebody else, they're not expending their resources very well.
>
> And so people in another company that don't own the compound wouldn't pursue those compounds because they know they wouldn't have a benefit to their company at the end.

(Press 174:16-23); *accord Brenner v. Manson*, 383 U.S. 519, 534 (1966) (footnote omitted) (Broad patents have the "power to block off whole areas of scientific development."); *id*. ("To the extent that the patentee has power to enforce his patent, there is little incentive for others to undertake a search for uses" of what is precluded by that patent.); *Princo Corp. v. Int'l Trade Comm'n*, No. 2007-1386, 2010 WL 3385953, at *27 (Fed. Cir. Aug. 30, 2010) (Dyk, J., dissenting) ("The mere threat of an infringement suit is typically sufficient to prevent a potential competitor from devoting the resources necessary to develop an alternative technology; the technology is thus suppressed at the outset.").

Because Otsuka's patents covered not only aripiprazole but also trillions of other carbostyril compounds, the most likely inference is that others stayed away from carbostyrils out of fearful respect for Otsuka's prior art patent portfolio. For example, Dr. Press, speaking from

personal experience, testified that when Lederle was faced with Eli Lilly's prior patent position on the drug olanzapine, Lederle was left "[w]ithout the ability to protect [its] work" and within a short time its "antipsychotic program was shut down." (Press 80:11-81:5, 190:8-20.) Prof. Nichols likewise testified that a pharmaceutical firm would likely not pursue a lead compound once it was learned that it was covered by someone else's patent. (Nichols 1712:17-1714:10.) In this case, Otsuka's pre-existing dominant patent position in carbostyrils undermines any inference that technical difficulties were the reason for why others did not develop aripiprazole or another carbostyril with the superiority alleged by Otsuka.

This analysis is not changed by the fact that some generic pharmaceutical firms *subsequently* sought *improvement* patents. Aripiprazole was approved by the FDA on November 15, 2002. (Jarosz 2112:3-7.) It was not until April 22, 2004, that the earliest of these other patent applications was filed. (PTX 659 (claiming a priority date of April 25, 2003); Press 317:18-24.) The most natural inference from this sequence of events is that aripiprazole's FDA approval triggered an interest in obtaining patents relating to improvements such as how to better manufacture the drug or how to better formulate it for better reception in the body. These later improvement efforts are not comparable to developing the new compound itself back in 1988. These later improvement patents in no way suggest that a large pharmaceutical firm would commit itself to developing a new drug knowing that a competitor's patents not only blocked sales but also interfered with getting one's own patent exclusivity. (Press 80:11-81:5; 190:8-20.) This is illustrated by Dr. Press's experience at Lederle where the olanzapine project was abandoned once it was learned that Eli Lilly had the dominant patent position. (Press 80:11-81:5; 190:8-20.) It is also corroborated by Otsuka's own internal policy of not pursuing the

development of compounds that cannot be patented because they are disclosed in prior art patents. (Oshiro 1826:20-1827:16.)

b. Alleged Copying.

Otsuka argues "copying" based on Defendants' ANDAs seeking to market generic forms of aripiprazole, but "a showing of copying is not compelling evidence of non-obviousness in Hatch-Waxman cases due to the nature of the ANDA process." *Santarus, Inc. v. Par Pharm., Inc.*, No. 07-551-GMS, 2010 WL 1506017, at *26 (D. Del. Apr. 24, 2010) (citations omitted). The Federal Circuit recently held that "evidence of copying in the ANDA context" is not compelling evidence of nonobviousness because "a showing of bioequivalency is required for FDA approval." *Purdue Pharma Prods. L.P. v. Par Pharm., Inc.*, Nos. 2009-1553, 2009-1592, 2010 WL 2203101, at *4 (Fed. Cir. June 3, 2010) (unpublished).

When a patentee asserts its patent is nonobvious because it was "copied" by a competitor, the inference that it seeks to draw is that the technical challenges were so great that success was beyond the reach of those of ordinary skill in the art. The requisite inference, however, simply cannot be drawn in the ANDA litigation context where the generic manufacturer's alleged "copying" behavior is a result of Hatch-Waxman Act incentives, not a failure to overcome some technical hurdle. *Aventis Pharma Deutschland GmbH v. Lupin Ltd.,* No. 2:05CV421, 2006 WL 2008962, at *45, *47 (E.D. Va. July 17, 2006) ("[T]he reason why Lupin attempted to copy Altace is because the ANDA process allows a generic drug company to challenge a drug patent by alleging the patent is invalid. . . . [G]iven that there is a statute in place that encourages generic drug companies to challenge patents, Aventis/King's copying argument is weak."), (holding patent not invalid, but with "reservations in doing so."), *rev'd*, 499 F.3d 1293 (Fed. Cir. 2007) (holding patent invalid for obviousness). Accordingly, Otsuka's "copying" allegations do not support a conclusion of nonobviousness.

c. Alleged Commercial Success.

The use of commercial success as a secondary indicium of nonobviousness is premised on an underlying inference that "an idea would successfully have been brought to market sooner, in response to market forces, had the idea been obvious to persons skilled in the art," and that "[i]f in fact a product attains a high degree of commercial success, there is a basis for inferring that such attempts have been made and have failed." *Merck & Co., Inc. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005). That inference cannot be drawn, and commercial success is not probative of non-obviousness, where there is a blocking patent position that discouraged others from exploiting the fruits of research in the field. *Merck*, 395 F.3d at 1377 ("Financial success is not significantly probative of that question in this case because others were *legally barred* from commercially testing the Lunar News ideas.") (emphasis added); *accord Syntex*, 407 F.3d at 1383.

Otsuka's prior patents covered aripiprazole, plus a large number of other carbostyril compounds. The very purpose of these patents was to discourage competitors. One is entitled to infer that these patents achieved their intended purpose of keeping competitors off Otsuka's carbostyril reservation. There is no basis for inferring that market forces drove others to try and then fail to develop a commercial aripiprazole product, which is the inference on which reliance upon commercial success would be based. Subsequent improvement patent activity by generic firms does not alter this conclusion because it does not relate to how a competing large pharmaceutical firm would have earlier gone about developing a new antischizophrenic compound in the first place.

The existence of Otsuka's prior '416 patent raises another difficulty with Otsuka's reliance on commercial success. Otsuka's expert, Mr. Jarosz, did not even attempt to determine the portion of success attributable to the invention in the '416 patent, or to other Otsuka patents

that cover aripiprazole. (Jarosz 2116:6-12; 2121:15-2133:4.) On this record, the Court cannot know how much, if any, effect to give to commercial success. *Syntex*, 407 F.3d at 1383 ("Assuming the active ingredient in the formulation was previously patented, the commercial success of ACULAR may heavily derive from subject matter that does not on the whole contribute to the patentable distinctiveness of these claims.").

The weight assignable to commercial success is further reduced by the evidence that Otsuka and its U.S. sales partner BMS paid fines for illegal sales practices involving Abilify®, because it would be inequitable and contrary to public policy to let Otsuka benefit from such actions. (Jarosz 2151:18-2156:9; DTX 1461; DTX 1462.)

In sum, there is no basis for drawing the inference of failed attempts by others that would justify reliance on commercial success as an indicium of nonobviousness. Even if commercial success were some how relevant without this inference, the record does not support assigning much, if any, weight to Abilify's sales.

d. Alleged Long-Felt Need and Failure of Others.

Otsuka argues that the development of aripiprazole solved a long-felt need for a safe and effective antipsychotic for the treatment of schizophrenia with reduced side effects. The relevance of long-felt need to obviousness relies on the inference that others must have tried and failed. That inference cannot logically be drawn here because others seeking to address the long-felt need would have been discouraged by Otsuka's blocking patent position. *Sanofi-Synthelabo v. Apotex Inc.,* 492 F. Supp. 2d 353, 392 (S.D.N.Y. 2007) ("Sanofi's ownership of the '596 patent precluded anyone else from bringing clopidogrel bisulfate to market throughout the duration of that patent. For that reason, evidence relating to the 'failure of others,' a 'long-felt but unsolved need,' [and other factors]" is undermined by the fact that those phenomena—to the extent they exist in this case—could have been derived from Sanofi's ownership of the '596

patent as much as from the nonobviousness of clopidogrel bisulfate."), *aff'd*, 550 F.3d 1075 (Fed. Cir. 2008).

Development by others was further restricted by the regulatory framework of the Hatch-Waxman Act and the high barriers to entry for parties seeking to market a new chemical entity. A scientist cannot simply develop a new drug treatment for schizophrenia and start selling it. Rather, the scientist must have the immense resources necessary for animal and then human testing, as well as an extensive marketing and sales force to satisfy the regulatory hurdles imposed by the FDA and then get the drug to market. Thus, the explanation for why others did not develop aripiprazole through the optimization of prior art carbostyril compounds (as Otsuka did) or conduct research into the potential use of carbostyril compounds is not the alleged nonobviousness of aripiprazole, but rather that Otsuka had already used patents to block out all others from pursuing this route and that the regulatory system erected barriers to entry faced by others seeking to market such a compound.

There were only a few months between the public disclosure of a critical piece of prior art—namely, the Nakagawa Declaration—that became available upon the issuance of the '416 patent in March 1988, and Otsuka's October 1988 Japanese filing date for the '528 patent. This short time period cuts against any inference of long-felt, but unsolved need. *Graham*, 383 U.S. at 36 (Unsuccessful efforts made before the availability of important prior art are "irrelevant."); *Carter-Wallace*, 474 F.2d at 546 ("[T]his is not a case where the directly relevant prior art was old and there had been long and unsuccessful struggles to meet the unfilled need. As the district court said, 341 F. Supp. at 1335, 'here the argument . . . is all but completely forestalled by the appearance at the last moment' of much of the relevant prior art.") (ellipsis in original).

Aripiprazole was not the first atypical antipsychotic to receive FDA approval for use in treating schizophrenia—it was actually the sixth atypical antischizophrenic drug to enter the United States market. (Jarosz 2090:15-20.) Five other FDA approved atypical antischizophrenics preceded aripiprazole to market, demonstrating that "different manufacturers with different drugs [had] succeeded in this business." (*Id.* at 2062:3-4.) They are clozapine (1990), risperidone (1994), olanzapine (1996), quetiapine (1997), and ziprasidone (2001). (Nichols 1586:15-1587:7.) After aripiprazole was approved, three additional atypical antipsychotics received FDA approval for treating schizophrenia—paliperidone (2007), iloperidone (2009), and asenapine (2009). (*Id.*)

The record thus shows that other drug manufacturers, blocked by Otsuka's patent position from developing carbostyril compounds as antipsychotic drugs, were able to successfully develop and obtain FDA approval for other atypical antipsychotic drugs for use in the treatment of schizophrenia before aripiprazole was approved. This undercuts any inference that others must have tried and failed to bring an atypical antischizophrenic drug to market. Instead, it demonstrates that the level of skill in the art was high enough to overcome any technical hurdles to successfully bringing an atypical antischizophrenic to market.

Accordingly, in view of all the evidence, Otsuka's assertion of long-felt and unsolved need does not support validity in this case.

e. Alleged Industry Acclaim.

Otsuka also relies on industry acclaim, such as the 2006 Prix Galien award for the development of aripiprazole. This and the other awards were presumably for the entire research effort made by Otsuka. There is, in any event, no evidence that the awarding authorities made any attempt to sort out the last increment of development that took the program from the portions of Otsuka's own work that is citable as prior art, such as OPC-4392 and the Nakagawa

Declaration, to aripiprazole. By contrast, under a § 103 analysis, Otsuka's own citable prior art work counts *against* patentability. *KSR*, 550 U.S. at 427 ("[A]dvances, once part of our shared knowledge, define a new threshold from which innovation starts once more."); *Condenser Corp. v. Micamold Radio Corp.*, 145 F.2d 878, 879 (2d Cir. 1944) ("[W]hatever the benefit which the inventor who takes a last step has in fact conferred, he will be credited only with the ingenuity necessary to pass beyond the earlier" steps that are part of the prior art citable against his invention.) (L. Hand). Accordingly, there is no correlation between these awards and the task required under § 103.

5. *Other Decisions Involving Other Antischizophrenic Drugs.*

a. The *Janssen* and *Eli Lilly* Cases Are Factually Different from the Case at Bar.

Otsuka relies on *Janssen Pharmaceutica N.V. v. Mylan Pharmaceuticals, Inc.*, 456 F. Supp. 2d 644 (D.N.J. 2006), where the court upheld the patent on the antischizophrenic drug risperidone. Another antischizophrenic drug case is *Eli Lilly & Co. v. Zenith Goldline Pharmaceuticals, Inc.*, 471 F.3d 1369 (Fed. Cir. 2006), that upheld the patent on olanzapine. Both cases provide background concerning the history of antischizophrenic drugs, but after that they are each quite different factually from the case at bar. For example, in *Janssen* the court rejected the defendant's argument based on the prior art pirenperone compound because the prior art taught that pirenperone was an anti-anxiety drug, not an antipsychotic. 456 F. Supp. 2d at 657. By contrast, in this case, the texts of Otsuka's prior art patents, the mouse jumping tests in the Nakagawa Declaration, and clinical tests in humans on OPC-4392 all indicate that carbostyrils have antischizophrenic potential. In *Eli Lilly* the defendants' obviousness argument ran counter to the accepted wisdom that an antipsychotic drug ought to have an electron-withdrawing group such as a fluorine or chlorine atom. 471 F.3d at 1374, 1378-79. By contrast,

in this case all of Defendants' arguments are consistent with the principle of having an electron withdrawing group (*i.e.*, chlorine).

There is yet another big difference between the case at bar and what happened in *Janssen* and *Eli Lilly*. Otsuka elected to publish about its own prior work on carbostyrils, including what happened in Phase I and II clinical trials on OPC-4392. That phase of the development of aripiprazole counts against, not for, patentability. In *Janssen* and *Eli Lilly* the hypothetical person of ordinary skill was not credited with comparable knowledge.

b. The Supreme Court's Landmark *KSR* Decision Changed Legal Principles Applied in *Janssen* and *Eli Lilly*.

Another difference between the present case and the *Janssen* and *Eli Lilly* cases is that those two cases were decided before the Supreme Court's landmark decision in *KSR*.

(1) The TSM Test.

KSR held that the Federal Circuit's "rigid" application of the "teaching, suggestion, or motivation" test (the "TSM" test) was inconsistent with the "expansive and flexible approach" required by Supreme Court precedent. 550 U.S. at 415. The Supreme Court warned, "Rigid preventative rules that deny fact finders recourse to common sense, however, are neither necessary under our case law nor consistent with it." *Id.* at 421. In *Janssen* and *Eli Lilly* the courts applied the old pre-*KSR* TSM test. *Eli Lilly*, 471 F.3d at 1378, 1379; *Janssen* 456 F. Supp. 2d at 655. One cannot know how these courts would have addressed obviousness issues in the post-*KSR* world.

(2) The Level of Skill.

KSR pointed out that another problem in taking an overly rigid approach to obviousness is a tendency to underestimate the ability of the hypothetical person of ordinary skill in the art. "A person of ordinary skill is also a person of ordinary creativity, not an automaton." 550 U.S.

at 421. Therefore, "a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* at 418. By contrast, the *Janssen* court stated that the person of ordinary skill in the art was "not one who undertakes to innovate," citing pre-*KSR* law. 456 F. Supp. 2d at 653. In the post-*KSR* world the hypothetical person of ordinary skill operates at a higher level of competence than was afforded by the *Janssen* and *Eli Lilly* courts.

(3) Obvious To Try.

KSR also found fault with the Federal Circuit's treatment of the concept of "obvious to try." 550 U.S. at 421 ("The same constricted analysis led the Court of Appeals to conclude, in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was 'obvious to try.'"). This concept is grounded on the common sense notion that if something was "obvious to try," then it would probably have been obvious to § 103's hypothetical person of ordinary skill in the art.

Since *KSR,* the Federal Circuit has made it clear that the notion of "obvious to try" is to be applied even to the so-called unpredictable arts. *E.g.*, *Bayer Schering Pharma AG v. Barr Labs., Inc.*, 575 F.3d 1341 (Fed. Cir. 2009) (using "obvious to try" analysis to invalidate patent on oral contraceptive drospirenone); *In re Kubin*, 561 F.3d 1351 (Fed. Cir. 2009) (using "obvious to try" analysis to invalidate patent on certain isolated polynucleotides). In *Kubin,* the Federal Circuit specifically "decline[d] to cabin *KSR* to the 'predictable arts.'" 561 F.3d at 1360. As the *Kubin* court saw it, "[T]he Supreme Court's admonition against a formalistic approach to obviousness in this context actually resurrects this court's own wisdom in *In re O'Farrell*, [853 F.2d 894 (Fed. Cir. 1988). . . ." 561 F.3d at 1359.

Under current Federal Circuit law something that is "obvious to try" is unpatentable for obviousness under § 103, unless one of two exceptions apply. *Kubin*, 561 F.3d at 1359 ("To differentiate between proper and improper applications of 'obvious to try,' this court outlined

two classes of situations where 'obvious to try' is erroneously equated with obviousness under § 103."). "First, an invention would not have been obvious to try when the inventor would have had to try all possibilities in a field unreduced by direction of the prior art." *Bayer,* 575 F.3d at 1347. "Second, an invention is not obvious to try where vague prior art does not guide an inventor toward a particular solution." *Id.* The core notion underlying both these exceptions is that if the prior art provides guidance as to what to try, then that which is "obvious to try" is invalid for obviousness—but if the prior art provides no guidance, so that the skilled person is left to trying things willy nilly, obviousness is not proved. These exceptions do not apply to the case at bar because the prior art provides direction about how to modify the structure of prior art carbostyrils to improve antischizophrenic potency.

Given that *Bayer* and *Kubin* establish that the notion of "obvious to try" applies even to the "unpredictable" arts, it cannot be said that the prior art must "predict" the claimed invention in order to have invalidity for obviousness. *Bayer*, *Kubin*, and *O'Farrell* each say that all that is required is "a reasonable expectation of success." *Bayer*, 575 F.3d at 1349; *Kubin*, 561 F.3d at 1360; *O'Farrell*, 853 F.2d at 904. In other words, the existence of some "uncertainty" does not preclude invalidity for obviousness. *Kubin*, 561 F.3d at 1360; *see also Carter-Wallace*, 474 F.2d at 546 ("The experimentation which is the essence of this art need not require a guarantee of success before a step can be obvious. . . ."). Thus, the fact that one has to test a compound to see if it works for its intended purpose does not negate obviousness. *Pfizer*, 480 F.3d at 1364.

In the post-*KSR*, post-*Kubin*, post-*Bayer* world, consideration must be given to an "obvious to try" analysis even in an unpredicatable art. There is no mention of "obvious to try" or the *O'Farrell* case in the *Janssen* or *Eli Lilly* opinions, and so there is no way of knowing how those courts would have dealt with the issue.

In the case at bar the evidence goes well beyond "obvious to try." Even if it did not, however, the asserted claims would be invalid. The selection of the linker length and substituent arrangement was a matter of merely optimizing known variables, which was well within the ordinary level of skill in this art. *Pfizer*, 480 F.3d at 1368; *see also Ruben Condenser Co. v. Aerovox Corp.*, 77 F.2d 266, 268 (2d Cir. 1935) (Patentability requires "something more than routine testing of obvious combinations.") (L. Hand).

6. *Conclusion on Obviousness.*

If the PTO had known about the Nakagawa Declaration and the Wise Poster, the examiner would have continued to reject the claims as obvious in view of the 2,3-dichloro propoxy compound. Furthermore, the claims are invalid because of the lack of patentable distinction between aripiprazole and the unsubstituted butoxy of Otsuka's own prior art '416 patent. In addition, it was well within the ability of a person of ordinary skill to obtain aripiprazole by carrying out a drug optimization program based on OPC-4392. A person of ordinary skill in the art could have started with any one of these prior art compounds, but would not have fixated on a particular one of them. Instead, the information from all the prior art compounds would be considered together and evaluated for what they teach as a collective whole. The convergence of these several approaches makes an overwhelming case of obviousness in view of the prior art genus that includes each of the aforementioned compounds. The Court concludes that aripiprazole is not patentably better than the prior art genus of carbostyril derivatives. Even if Otsuka's allegations of secondary considerations were probative of some inference of nonobviousness (they are not), they would not be sufficient to overcome this strong evidence of obviousness. *Pfizer*, 480 F.3d at 1372 (strong showing of obviousness not overcome by secondary considerations); *Newell*, 864 F.2d at 768 (same).

Aripiprazole was the last episode in years of work by Otsuka. Most of this work was put into the public domain before the '528 patent's October 31, 1988 priority date by Otsuka's own extensive patent activities (such as the '416 patent, its foreign counterparts, and other patents in the carbostyril field) and scientific articles reporting Otsuka's testing of carbostyril compounds in both animals and humans. Thus, most of Otsuka's work leading to aripiprazole counts *against, not for*, patentability because it is part of the citable prior art. *KSR*, 550 U.S. at 427; *Condenser v. Micamold*, 145 F.2d at 879. The final increment of effort needed to get to aripiprazole involved no more than "ordinary innovation" that is "not the subject of exclusive rights under the patent laws." *KSR*, 550 U.S. at 427. Indeed, no innovation was required, because only routine optimization of prior art compounds was involved. *Pfizer*, 480 F.3d at 1367-68.

Accordingly, claim 12 to the compound itself is invalid for obviousness. Claim 17 to a pharmaceutical composition containing aripiprazole for treating schizophrenia and claim 23 to a method of treating schizophrenia with aripiprazole are also invalid for obviousness because that is exactly what the hypothetical person of ordinary skill in the art would have done with aripiprazole: the whole point of modifying the prior art carbostyril derivatives was to optimize their antischizophrenic characteristics.

E. THE '528 PATENT IS UNENFORCEABLE FOR INEQUITABLE CONDUCT.

1. *The Legal Standard.*

Persons involved in the preparation and prosecution of a patent application "have a duty to prosecute patent applications in the [PTO] with candor, good faith, and honesty." *Advanced Magnetic Closures, Inc. v. Rome Fastener Corp.*, 607 F.3d 817, 829 (Fed. Cir. 2010) (quoting *Honeywell Int'l Inc. v. Universal Avionics Sys. Corp.*, 488 F.3d 982, 999 (Fed. Cir. 2007)). This duty of candor rests on "(1) each named inventor, (2) each attorney or agent that prepares or

prosecutes the application, and (3) every other person who is substantively involved in the preparation or prosecution of the application and who is associated with the inventor or assignee." *Avid Identification Sys., Inc. v. Crystal Import Corp.*, 603 F.3d 967, 973 (Fed. Cir. 2010) (citing 37 C.F.R. § 1.56(c)). A breach of the duty of candor constitutes inequitable conduct and renders the patent unenforceable. *Bristol-Myers Squibb v. Rhone-Poulenc Rorer, Inc.*, 326 F.3d 1226, 1233 (Fed. Cir. 2003); *Molins PLC v. Textron, Inc.*, 48 F.3d 1172, 1178 (Fed. Cir. 1995).

Unenforceability of a patent due to inequitable conduct is based on the equitable principle that the courts will not grant relief to a plaintiff with unclean hands.

> The guiding doctrine in this case is the equitable maxim that 'he who comes into equity must come with clean hands.' This maxim is far more than a mere banality. It is a self-imposed ordinance that closes the doors of a court of equity to one tainted with inequitableness or bad faith relative to the matter in which he seeks relief, however improper may have been the behavior of the defendant.

Precision Instrument Mfg. Co. v. Automotive Co., 324 U.S. 806, 814 (1945); *accord Keystone Driller Co. v. Gen. Excavator Co.*, 290 U.S. 240, 241 (1933). In the patent context, this doctrine serves to protect not only parties but also the public interest:

> [T]hese are matters concerning far more than the interests of the adverse parties.
>
> * * *
>
> A patent by its very nature is affected with a public interest. As recognized by the Constitution, it is a special privilege designed to serve the public purpose of promoting the 'Progress of Science and useful Arts.' At the same time, a patent is an exception to the general rule against monopolies and to the right to access to a free and open market. The far-reaching social and economic consequences of a patent, therefore, give the public a paramount interest in seeing that patent monopolies spring from backgrounds free from fraud or other inequitable conduct and that such monopolies are kept within their legitimate scope.

Precision, 324 U.S. at 815-16; *accord Hazel-Atlas Glass Co. v. Hartford-Empire Co.*, 322 U.S. 238, 246 (1944) ("This matter does not concern only private parties. There are issues of great moment to the public in a patent suit.").

Application of the doctrine of unclean hands is flexible and is not confined to any particular kind of offending activities.

> This maxim necessarily gives wide range to the equity court's use of discretion is refusing to aid the unclean litigant.
>
> * * *
>
> Any willful act concerning the cause of action which rightfully can be said to transgress equitable standards of conduct is sufficient cause for the invocation of the maxim by the chancellor.

Precision, 324 U.S. at 815; *accord Keystone*, 290 U.S. at 245-46 ("not bound by formula or restrained by any limitation that tends to trammel free and just exercise of discretion"). Under Federal Circuit precedent, inequitable conduct requires proof of (1) failure to disclose information or submission of false information to the PTO; (2) materiality of the withheld or false information ; and (3) an intent to deceive. *Advanced Magnetic*, 607 F.3d at 829; *McKesson Info. Solutions, Inc. v. Bridge Med., Inc.*, 487 F.3d 897, 913 (Fed. Cir. 2007).

Information is material when a reasonable examiner would likely consider the information important in deciding whether to allow the patent to issue. *Advanced Magnetic*, 607 F.3d at 829; *Avid*, 603 F.3d at 972. Thus, information concealed from the PTO may be material "even if that piece of information does not actually invalidate the patent." *Avid*, 603 F.3d at 973. Moreover, "[a] withheld reference may be highly material when it discloses a more complete combination of relevant features, even if those features are before the patent examiner in other references." *Semiconductor Energy Lab. Co. v. Samsung Elecs. Co.*, 204 F.3d 1368, 1374 (Fed. Cir. 2000). When a question of materiality is close, the patent applicant is required to err on the side of disclosure. *See LaBounty Mfg. v. U.S. Int'l Trade Comm'n*, 958 F.2d 1066, 1076 (Fed. Cir. 1992) ("Close cases should be resolved by disclosure, not unilaterally by the applicant.").

Proof of intent "does not require direct evidence; it can be inferred from indirect and circumstantial evidence." *Taltech Ltd. v. Esquel Enters. Ltd.*, 604 F.3d 1324, 1332 (Fed. Cir.

2010); *see also Paragon Podiatry Lab., Inc. v. KLM Labs., Inc.*, 984 F.2d 1182, 1189 (Fed. Cir. 1993) ("'[S]moking gun' evidence is not required in order to establish an intent to deceive."); *Merck v. Danbury Pharmacal, Inc.*, 873 F.2d 1418, 1422 (Fed. Cir. 1989) ("Intent need not, and rarely can, be proven by direct evidence."). Moreover, a patent applicant or an attorney cannot cultivate ignorance. *Brasseler, U.S.A. I, L.P. v. Stryker Sales Corp.*, 267 F.3d 1370, 1383 (Fed. Cir. 2001). Those who have a duty of candor must conduct meaningful inquiries when the surrounding facts and circumstances indicate the need for such an inquiry. *Id.* at 1385. If a patentee fails to offer a credible explanation for its nondisclosure, the court may infer an intent to deceive the PTO. *Bruno Indep. Living Aids, Inc. v. Acorn Mobility Servs., Ltd.*, 394 F.3d 1348, 1354-55 (Fed. Cir. 2005).

Finally, once the court determines that an omission or false statement is material and was made with intent to deceive, the Court must balance materiality and intent. *Taltech*, 604 F.3d at 1328; *McKesson*, 487 F.3d at 913. Where an omission or misrepresentation is highly material, less evidence of intent will be required in order to find that inequitable conduct has occurred. *Id.*

The future of the Federal Circuit's law of inequitable conduct is uncertain. On November 9, the Federal Circuit will hear argument en banc on legal questions relating to it. *Therasense, Inc. v. Becton, Dickinson & Co.*, 2010 WL 1655391 (Fed. Cir. Apr. 26, 2010) (ordering rehearing en banc), 2010 WL 2203531 (Fed. Cir. June 3, 2010) (setting argument on November 9). Although it is quite possible that after *Therasense* is decided en banc the law may be different, the Court must decide the case based on the law as it presently stands.

2. *False and Withheld Information and Its Materiality.*

Defendants allege that Otsuka committed inequitable conduct during the prosecution of the reexamination of the '528 patent through a series of failures to submit information and submission of false information to the PTO. This conduct involved (1) withholding internal

Otsuka data that is inconsistent with the results and conclusions presented in the Hirose Declaration and false statements in the Hirose Declaration regarding the protocol used to generate the data presented in it, (2) failure to submit the Nakagawa Declaration, and (3) false statements in the prosecution history. The withheld information and false statements in the declaration are material because they directly contradict the essential argument that secured allowance of the '528 patent during reexamination: that the change from a propoxy linker to a butoxy linker allegedly resulted in an "unexpected" improvement in antipsychotic activity. (DTX 121 at 01412; DTX 4 at OPC0001624-OPC0001625; DTX 399; Hirose 1979:4-1980:16; Press 168:10-169:11.)

a. The Hirose Declaration.

Dr. Hirose's declaration was crucial evidence that convinced the reexamination examiner that the change from a propoxy linker to a butoxy linker yielded "unexpected" superiority. It reported head to head comparisons of claimed compounds, (*e.g.*, aripiprazole), and their propoxy homologues (*e.g.*, 2,3-dichloro propoxy). In her Reasons for Patentability/Confirmation, the Examiner stated:

> The compounds [of] claims 1-21 are found to be allowable since applicants have compared their compounds with the closest prior art. The ones with just one difference in the linker chain, propyloxy [i.e., propoxy] to a butoxy chanin [sic, chain] shows a clear unexpected result in the ED50 values.

(DTX 121 at 01412.)

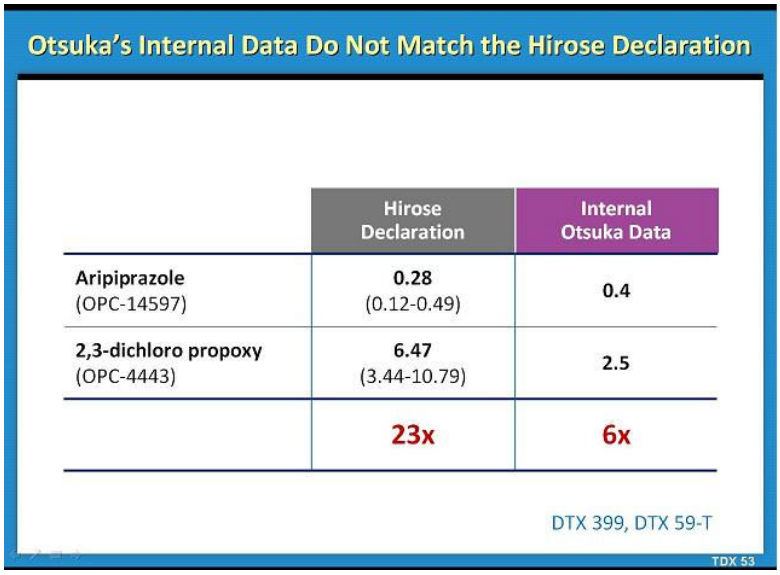
The Federal Circuit has made clear that misrepresentations contained in affidavits or declarations submitted to the PTO are *per se* material. *Refac Int'l, Ltd. v. Lotus Dev. Corp.*, 81 F.3d 1576, 1583 (Fed. Cir. 1996) ("Affidavits are inherently material."); *Rohm & Haas Co. v. Crystal Chemical Co.*, 722 F.2d 1556, 1571 (Fed. Cir. 1983) ("In contrast to cases where allegations of fraud are based on the withholding of prior art, there is no room to argue that

submission of false affidavits is not material."). In addition, courts have repeatedly held that the failure to provide unfavorable test results is material. *E.g.*, *Grefco, Inc. v. Kewanee Indus., Inc.*, 499 F. Supp. 844, 870 (D. Del. 1980), *aff'd*, 671 F.2d 495 (3rd Cir. 1981); *see also Mead Johnson & Co. v. Premo Pharm. Labs.*, 207 U.S.P.Q. 820, 851 (D.N.J. 1980) ("The degree of responsibility imposed upon an inventor for disclosure is maximized when the invention is intended to treat human disorders. The existence of other governmental agencies to perform similar functions in no way reduces the obligation imposed upon him in connection with his application for a patent."). This is because an applicant's duty to disclose information includes highlighting, or "red-flagging," contradictory information that comes from its own test results. *Golden Valley Microwave Foods, Inc. v. Weaver Popcorn Co.*, 837 F. Supp. 1444, 1475 (N.D. Ind. 1992), *aff'd*, 11 F.3d 1072 (Fed. Cir. 1993).

The Hirose Declaration was prepared by Dr. Hirose in conjunction with Otsuka's lawyers, including attorneys from the Finnegan firm, and Dr. Oshiro. In particular, Dr. Oshiro testified at trial that he was involved in meetings relating to the reexamination of the '528 patent and that he reviewed and edited the Hirose Declaration. (Oshiro 1896:9-1897:6.) Dr. Hirose also testified that he attended ten or more meetings relating to the reexamination prior to the submission of the declaration, and that those meetings always included the "core group," of Drs. Oshiro, Kikuchi, Yamamoto and Minimikawa, and occasionally included a statistician and members of the Finnegan firm. (Hirose 1916:11-23.) This "core group" comprised Otsuka employees with expertise in pharmacology, organic chemistry, intellectual property, and statistics." (Hirose 1914:9-1918:3.) By the time the meetings were concluded Dr. Hirose knew that his task was to show that the compounds claimed in the '528 patent were superior to the prior art compounds. (Hirose 1976:11-1980:13; 1986:8-14; Thisted 1471:2-4.)

(1) Otsuka's Withheld Contradictory Internal Data.

During the investigation that led to the selection of aripiprazole, Dr. Oshiro had already made a comparison of claimed compounds to prior art compounds similar to the comparison found in the Hirose Declaration. In particular, he had generated data comparing aripiprazole to its propoxy homolog, the 2,3-dichloro propoxy compound, and had presented it in an internal year-end presentation to Otsuka. (DTX 59-T at OPC0717014; Oshiro 1901:2-20.) In this earlier internal data, the 2,3-dichloro propoxy compound (OPC-4443) showed an ED_{50} value of 2.5 mg/kg, a much better ED_{50} value than the 6.47 mg/kg ED_{50} value reported in the Hirose Declaration. (DTX 59-T at OPC0717014; Oshiro 1900:24-1901:7.) Aripiprazole (OPC-14597) showed an ED_{50} value of 0.4 mg/kg, a worse ED_{50} value than the 0.28 mg/kg value reported in the Hirose Declaration. (DTX 59-T at OPC0717014; Oshiro 1901:8-20.) Thus, in Dr. Oshiro's tests, instead of the 23-fold difference claimed in the Hirose Declaration, aripiprazole was only six times better than the 2,3-dichloro propoxy compound. (DTX 399, Table 1; Oshiro 1902:2-1903:7.) A comparison of Otsuka's internal data and the data in the Hirose Declaration for aripiprazole and its 2,3-propoxy homolog appears below.



(TDX 53 (citing DTX 399, DTX 59-T.) As discussed in Section III(I)(2), Dr. Oshiro testified at trial that a mere six-fold difference in potency between a propoxy compound and a butoxy compound is not a considerable or surprising improvement. (Oshiro 1772:12-1773:3; 1843:21-1845:9; PTX 35-T.) In particular, on direct examination Dr. Oshiro testified that improvement in anti-apomorphine stereotypy potency that he observed when changing the propoxy linker of OPC-4392 to a butoxy linker was neither considerable nor surprising. (Oshiro 1772:12-1773:3) On cross, Dr. Oshiro noted that that difference was six fold. (Oshiro 1843:21-1845:9; PTX 35-T.)

These internal data, particularly when viewed in light of co-inventor Oshiro's evaluation of them, contradict Otsuka's argument to the PTO—namely, that the claims covering aripiprazole are patentable because aripiprazole allegedly shows unexpected superiority over the prior art. Dr. Oshiro, however, did not disclose this contradiction to the PTO. A reasonable examiner would have considered these data and Dr. Oshiro's evaluation of them to be important to the patentability determination. This information was therefore material. Neither Dr. Oshiro, nor any Otsuka witness, offered an explanation as to why it would not be material, or why it was not disclosed to the PTO.

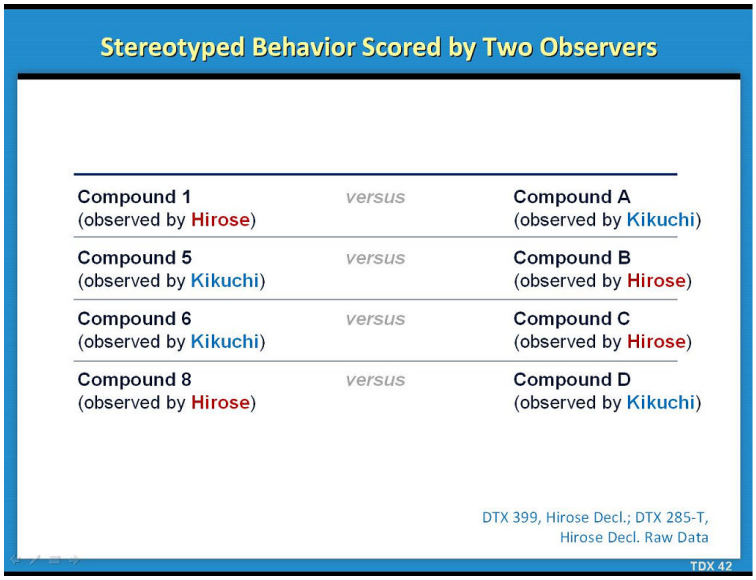
Dr. Oshiro was well aware of his duty of candor. As an inventor of both of the '416 patent and the '528 patent, Dr. Oshiro has signed two declarations in which he acknowledged his duty of candor pursuant to 37 C.F.R. § 1.56. (DTX 333-A; DTX 116 at OPC0000049 ("I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, § 1.56 .").) Dr. Oshiro testified that when he reads declarations, he makes sure to understand his duties, even if it

requires the help of others. (Oshiro 1894:4-1895:15.) Thus, Oshiro knew he had a duty to disclose the material information from his presentation to the PTO.

In addition, although Dr. Hirose testified that he did not know whether he had previously compared aripiprazole to the 2,3-dichloro propoxy, he testified that he was involved in the testing of aripiprazole in 1987. (Hirose 1920:3-7.)

(2) False Statements in the Hirose Declaration.

Otsuka's undisclosed contradictory internal data is also material because it supports the possibility that the data submitted in the Hirose Declaration were affected by flaws in the experimental methodology which were hidden from the Examiner by false statements made in the declaration. (DTX 4.) Study Protocol 023155 attached as Exhibit 1 to the Hirose Declaration reads that "[t]he observation for stereotyped behavior will be performed by *an observer blind to the treatment received by the mice*." (DTX 399, Ex. 1 at 9 (emphasis added).) A reasonable examiner would have understood the protocol to mean that only one observer scored the stereotyped behavior for all the claimed and prior art compounds and that that observer did not know what compound was being used to treat the mice under observation. (Beninger 957:18-958:8; 958:9-13.) However, the evidence at trial demonstrated that two observers—Drs. Hirose and Kikuchi—scored stereotyped behavior and that for each claimed compound and its comparative prior art compound, one person observed and scored the anti-stereotypy effect of the claimed compound and another person observed and scored the anti-stereotypy effect of the prior art compound, as shown in the chart below. (Beninger 936:25-937:23.)



(TDX 42 (citing DTX 399, DTX 285-T.) Thus, Dr. Hirose scored the anti-stereotypy effect of aripiprazole, whereas Dr. Kikuchi scored the anti-stereotypy effect of the 2,3-dichloro propoxy compound. (Beninger 937:11-14; Hirose 1986:8-14.) The evidence also shows that the observers were not blind to the compound being tested and that they both knew the purpose of the experiment. (Beninger 947:5-10; Thisted 1471:2-4; Hirose 1930:20-1931; 1986:8-14; Roth 1302:14-21.)

A reasonable examiner would have considered it important to know how Dr. Hirose actually performed the stereotypy test in order to be able to assess the reliability of the results. As discussed in Section III(H)(1), the actual methodology of Dr. Hirose's experiment was flawed because due to the subjectivity of the scoring scale, it introduced both confound and bias into the experiment, rendering the data uninterpretable. (Beninger 929:11-21; 956:7-11.) From the protocol that Otsuka submitted to the PTO, the examiner would not have been aware that two observers were involved or that the observers were aware of the identity of the compound that was used to treat the mice they were observing. (Beninger 932:1-7; 958:17-959:2; Thisted 1503:16-24.) The false statements in the declaration were therefore material.

Otsuka advances several arguments in its defense. First it cries no harm, no foul. It argues that the test results in fact were not affected by confounding or bias. (Thisted 1438:18-1439:15.) As Defendants' experts maintain, it is not possible to ascertain whether or not the tests results were affected by the confound or bias. (Beninger 945:21-946:1; 947:5-17; 954:22-955:10.) In any case, this argument is irrelevant here because the issue is whether a reasonable examiner would have considered this information to be important. (Goolkasian 477:20-478:10.) It would have. (Goolkasian 524:3-18; Beninger 958:17-959:2.) If the PTO had known of the potential for confounding and bias, it would not have relied on Dr. Hirose's declaration as filed.

Second, Otsuka argues that the use of two observers was disclosed because the protocol's signature page lists two "investigators." This argument, too, must be disregarded. Nowhere does the protocol state that the two investigators would both function as observers. Given the statement in the methods section of the protocol that "[t]he observation for stereotyped behavior will be performed by *an observer* blind to the treatment received by the mice" the Examiner would have assumed that only one of the investigators was observing. (DTX 399, Ex. 1 at 9 (emphasis added).)

Finally, Dr. Hirose states that the language "blind to the treatment received by the mice" merely meant blind to the dosage being given but not blind to the compound. (Hirose 1930:1-1931:4.) This is contrary to both Defendants' and Otsuka's experts' understanding of that phrase. Further, Dr. Hirose's testimony in defense of his experiment lacks credibility. During his testimony, Dr. Hirose clearly testified that the scoring scale was subjective, but after he was asked the question again he changed his answer. (Hirose 1935:21-1937:10.)[16]

[16] It was at this point that the Court instructed that "no one is to communicate with a testifying witness, whether verbally or nonverbally . . . spectators are to remain immobile." (Tr. 1936:18-1937:3, Aug. 25, 2010.)

b. The Nakagawa Declaration.

There is no dispute that Otsuka did not disclose the Nakagawa Declaration. Accordingly, this item falls into the category of withheld prior art. Moreover, it was *highly material* prior art. Otsuka was able to obtain the '528 patent by convincing the examiner that the change from a propoxy linker to a butoxy linker resulted in an "unexpected" improvement in antipsychotic activity. (DTX 121 at 01412; *see* DTX 4 at OPC0001624-OPC0001625; DTX 399; Hirose 1979:4-1980:16; Press 168:10-169:11.) It also specifically argued that "there is no prior art evidence that the five exemplary carbostyril derivatives identified by the Examiner have the suggested properties, let alone the recited property of treating schizophrenia." (DTX 121 at 01274, 01348; Goolkasian 500:10-501:3.) The five exemplary compounds identified by the examiner include the unsubstituted butoxy and the 2,3-dichloro propoxy compound. (Oshiro 1880:20-1881:14; 1882:6-1882:15; 1883:15-1884:4; DTX 121 at 01274, 01280, 01348; DTX 459 at OPC0001554, OPC0001560.) Otsuka could not have taken this position or made these statements had it disclosed the Nakagawa Declaration to the PTO. The Nakagawa Declaration reports that the unsubstituted butoxy (and the 5-linked 2-ethoxy propoxy) was "excellent" in the Mouse Jumping Test for antischizophrenic activity. (DTX 214 at 14; *see* DTX 121 at 01249; Press 138:5-7.) It also contains SAR information that teaches that improvement in antipsychotic potential is obtained by changing from a propoxy to a butoxy linker and including chlorines at the 2 and 3 positions. A reasonable examiner would have considered the Nakagawa Declaration to be very important to the patentability examination. The Nakagawa Declaration was therefore highly material.

Dr. Oshiro, an inventor on the '416 patent, testified that he did not know of the Nakagawa Declaration. (Oshiro 1862:1-9.) Even if Dr. Oshiro had not been aware of the Nakagawa Declaration, he was aware of Mouse Jumping Test data for the unsubstituted butoxy,

one of the compounds for such data provided in the Nakagawa Declaration. (Oshiro 1865:2-1867:6.) In fact, Dr. Nakagawa, the declarant of the Nakagawa Declaration and formerly Dr. Oshiro's boss, testified in deposition that Dr. Oshiro likely worked on the data underlying the Nakagawa Declaration. (DTX 208-T; Oshiro 1860:25-1861:5; Nakagawa Dep. 140:21-25.)

There can be no doubt, however, that at least Otsuka's attorneys knew about the Nakagawa Declaration. It was Otsuka, through its attorneys at the Finnegan firm, that submitted the Nakagawa Declaration to the PTO during the prosecution of the '416 patent. (DTX 6 at OPC0793783; DTX 498 at p. 1; *see* Van Horn Dep. 18:2-8.) It is extremely unlikely that Mr. Van Horn, the Finnegan attorney who prosecuted the reexamination application, did not know of the Nakagawa Declaration. That declaration was submitted by members of his own firm during the prosecution of the principal prior art patent reference that he was arguing about during reexamination. Further, he had numerous communications with Otsuka personnel, including meetings both in Washington and in Japan, and no one other than Dr. Oshiro testified to lack of knowledge of the Nakagawa Declaration. (Hirose 1915:9-20; 1917:4-10; 1917:23-1918:13; 1972:4-17; *see* Van Horn Dep. 32:4-33:2.) Mr. Van Horn was listed by Otsuka as a trial witness, but he was not called to the stand. (D.I. 328 at 133 ¶ 3.) In these circumstances, where Otsuka had control over the witnesses who know what happened, the fact finder may draw the inference that the testimony they would have given would have been adverse to Otsuka. *A.B. Dick Co. v. Burroughs Corp.*, 798 F.2d 1392, 1400 n.9 (Fed. Cir. 1986); *accord Brasseler, U.S.A. I, L.P. v. Stryker Sales Corp.*, 267 F.3d 1370, 1384 n.7 (Fed. Cir. 2001).

c. Otsuka's Statements That There Was No Data Showing That the "Five Exemplary Compounds" Had Antischizophrenic Activity Were False.

During the reexamination, Otsuka represented to the PTO multiple times that there was no evidence that the five exemplary carbostyril derivatives of the '416 patent, which the

examiner based in part her rejections of the '528 patent claims, had antischizophrenic activity. (DTX 121 at 01274, 01348; DTX 459 at OPC0001554; Goolkasian 500:10-501:3.) Yet, Otsuka had prior art data indicating that at least two of these compounds had antischizophrenic activity.

The five exemplary carbostyril derivatives of the '416 patent that the examiner identified are Examples 29, 36, 43, 50, and 54 in the '416 patent. (DTX 121 at 01272-73.) Of these compounds, Otsuka knew that at least Examples 43 and 54 had prior art antischizophrenic activity.

Example 43 is the 5-linked 2-ethoxy propoxy and test compound no. 44 in the Nakagawa declaration. (Oshiro 1881:16-18; Nichols 1655:19-1656:4; DTX 214 at 14.) Example 43 has an ED50 value of 0.53 in the Mouse Jumping Test. (DTX 214 at 14.) Dr. Nichols testified that Example 43 was the most potent compound in the Mouse Jumping Test in the Nakagawa Declaration. (Nichols 1655:19-1656:4; DTX 214 at 14.)

Example 54 is the unsubstituted butoxy and test compound no. 41 in the Nakagawa declaration. (Press 133:5-7; Oshiro 1865:10-1866:3; Oshiro 1881:11-14; DTX 214 at 14.) Example 54 has an ED50 value of 5.5 in the Mouse Jumping Test. (DTX 214 at 14.) Dr. Oshiro had been aware of Otsuka's Mouse Jumping Test data for Example 54. (Oshiro 1867:2-6.)

Otsuka, therefore, knew that its representations to the PTO regarding the five exemplary carbostyril derivatives not having antischizophrenic activity were false and misleading. Dr. Oshiro, in particular, was aware of least Example 54 having antischizophrenic activity.

When these representations were made to the PTO, Dr. Oshiro was serving as an advisor to Otsuka's intellectual property department. (Oshiro 1793:17-23.) Dr. Oshiro attended at least ten meetings concerning the reexamination. (Hirose 1914:9-21; 1916:20-23; 1917:4-10; 1917:23-1918:3; 1972:4-17.) And as Otsuka's privilege log indicates, Dr. Oshiro had over 300

communications with Otsuka's intellectual property department and/or Otsuka's counsel Finnegan Henderson related to the reexamination proceedings. (DTX 61-A; see Oshiro 1877:15-1880:18; Hirose 1915:3-19.) In fact, on May 16, 2005 and September 14, 2005, the very days Otsuka filed amendments to the PTO in which it represented that the five exemplary compounds had no antischizophrenic activity, Dr. Oshiro communicated with Otsuka's intellectual property department regarding the reexamination. (DTX 61-A at 16, 40-41; DTX 121 at 01288, 01364; Oshiro 1880:5-18.) It is indisputable that Dr. Oshiro was highly involved in the reexamination, from before the reexamination began until after the reexamination finished. (See DTX 61-A; Oshiro 1877:11-1880:18.) Indeed, Dr. Oshiro could not deny having involvement with the amendment filed May 16, 2005, which stated that there was "no evidence" that the five exemplary compounds had antischizophrenic activity. (Oshiro 1891:24-1893:9; DTX-121 at 01274.)

The information that some of the five exemplary compounds had antischizophrenic activity was material because such information "refutes, or is inconsistent with, a position [Otsuka took] in . . . [a]sserting an argument of patentability." (37 C.F.R. § 1.56(b); Goolkasian 517:21-518:8; 37 C.F.R. § 1.555.)

3. *Intent.*

In real life no one stands up and confesses guilt. Of necessity it is circumstantial evidence that reveals an intent to deceive. In this case the record reveals a pattern of deceit involving suppression of material information that would have contradicted the very argument that secured allowance during reexamination, based on a sworn declaration containing a crucial false statement. The Federal Circuit has repeatedly found that the submission of a false statement to the PTO will support an inference of intent to deceive. As the Federal Circuit explained in *Paragon*: "The inference [of intent to deceive] arises not simply from the

materiality of the affidavits, but from the affirmative acts of submitting them, their misleading character, and the inability of the examiner to investigate the facts." 984 F.2d at 1191; *see also General Electro Music Corp. v. Samick Music Corp.*, 19 F.3d 1405, 1411 (Fed. Cir. 1994) ("'While direct proof of intent to mislead is normally absent, [the submission of a false or misleading statement] usually will support the conclusion that the affidavit in which they were contained was the chosen instrument of an intentional scheme to deceive the PTO.'") (quoting *Rohm & Haas*, 722 F.2d at 1571).

Moreover, other than claiming ignorance or memory loss in some instances, Otsuka made no attempt to explain why this information was not submitted to the PTO. For example, Dr. Oshiro, who was deeply involved in the reexamination process including the preparation of the Hirose Declaration, despite admitting that he was aware of the inconsistent test data since 1987, did not explain why he did not submit that prior internal data to the PTO. "[I]n the absence of a credible explanation, intent to deceive is generally inferred from the facts and circumstances surrounding a knowing failure to disclose material information" since "[n]ormally, it can be expected that an innocent party will be motivated to try to present convincing reasons for its actions or inaction." *Bruno*, 394 F.3d at 1354.

Furthermore, Dr. Oshiro had motivation to mislead the PTO during reexamination as both an employee who at the time of the reexamination was an advisor in the intellectual property department, and as an inventor who received milestone payments for the invention. (Oshiro 1746:23-1747:24; 1793:17-23; 1795:2-5; *see* Kurahashi Dep. 131:12-13; 131:15; 132:2-3; 132:6-11.) Therefore, one can infer that at least Dr. Oshiro intended to deceive the PTO.

With respect to the false statements in the Hirose Declaration, Dr. Hirose, Dr. Oshiro, and Finnegan attorneys were aware of the purpose of the experiments and put considerable effort into

devising and reporting them. It would have been very easy to avoid the underlying confound and bias problems, yet the only explanation given at trial as to why it was not done, was that it would have added an additional "level of complexity." (Thisted 1466:24-1468:7; 1500:21-24; Beninger 956:20-957:3; 1500:21-24; Roth 1303:19-1304:10.) It would have also been easy to accurately inform the Examiner about how the experiment was actually conducted. (*See* Roth 1115:9-18 (stating that when an experiment is not blinded, "usually you want to—basically you want to specify what is going on".) Otsuka offered no convincing explanation for this failure as well. One can therefore infer that Dr. Oshiro, Dr. Hirose, attorneys at the Finnegan firm, and others in Otsuka's "core group" intended to deceive the PTO by adopting an experimental methodology that would guarantee the results they needed and then hiding its flaws from the PTO.

With respect to the omission of the Nakagawa Declaration, for the reasons mentioned above, it is inconceivable that those involved with the prosecution of the reexamination were not aware of the Nakagawa Declaration given the extensive preparation that was undertaken in preparation for the filing of the reexamination application. The Nakagawa Declaration was part of the prosecution history of one of the principal prior art references forming the basis of Otsuka's reexamination request and names Dr. Oshiro as an inventor. Dr. Nakagawa was Dr. Oshiro's boss in the synthesis department at Otsuka. (Oshiro 1860:25-1861:5.) The absence of testimony by Mr. Van Horn or any explanation as to why this document was not brought to the attention of the examiner allows one to infer that it was withheld with intent to deceive.

Finally, with respect to the representations that the five exemplary compounds of the '416 patent did not have antischizophrenic activity, Dr. Oshiro's heavy involvement with the reexamination, his knowledge that some of the exemplary compounds had antischizophrenic activity, and the absence of testimony as to why this information was not disclosed to the

examiner allows one to infer that Dr. Oshiro withheld material information with an intent to deceive the PTO.

4. ***Balancing of Materiality and Intent.***

The Court concludes that it would be inequitable to enforce the '528 patent-in-suit. In this case the PTO was induced to allow the patent during reexamination based on argument that could not have prevailed if all of the material information had been provided to the PTO. The level of materiality is therefore very high. The Court is not persuaded that Otsuka's conduct can be explained by innocent motives or negligence, either simple or gross, particularly in the absence of relevant testimony by witnesses that Otsuka could have called to testify. Rather, it appears to this Court that Otsuka intentionally deceived the PTO. In such circumstances, the patent is too tainted to be enforced.

V. CONCLUSION.

The '528 patent claims to aripiprazole and its use for treating schizophrenia are held invalid and unenforceable.

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Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on September 27, 2010, a true and correct copy of the foregoing DEFENDANTS' POST-TRIAL PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW was served upon all counsel of record by the email system on:

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